F.R. Matthias

Blood Coagulation Disorders

Hemorrhagic Diatheses and Thromboembolic Diseases

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Prof. Dr. med. Fritz Reinhard Matthias
Department of Internal Medicine
Justus Liebig-University, Klinikstraße 36, 6300 Gießen
Federal Republic of Germany

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Foreword

This book on hemorrhagic diseases and thrombosis brings the reader up to date with the progress that has been made in one of the rapidly expanding fields in medicine. Although many of the topics discussed are in fact not of recent vintage they have again become a center of interest. They are related to the major changes arising from the new methods of diagnosis that have become available in the clinical laboratory and which are now being applied with greater precision and on a larger scale. The considerable progress that has been made in treatment, particularly of the almost ubiquitous thrombotic disorders, is also described.

Professor F. R. Matthias has his roots in a well-established hematological center. He has attempted to integrate both preclinical and clinical studies in a way that provides a logical and easily understood account of hemostasis and thrombosis, two distinct but interwoven areas of hematology; and he has succeeded. Moreover, he has written the book in a style which is easily comprehensible. Remembering that history does not repeat itself but that historians do, he has freed himself from the fetters of lengthy historial material and tedious repetition and has produced for his readers an enlightening, articulate, and well illustrated book.

Professor M. Verstraete
Director, Center of Thrombosis
and Vascular Research, University of Leuven, Belgium

Foreword

Disorders of hemostasis play a role in the pathogenesis of the most varied clinical syndromes. Moreover, it is not only thrombotic occlusion syndromes in the arteries or veins, or congenital or acquired hemorrhagic diatheses which definitely require knowledge of the relationships in clinical symptomatology. The results of the research of the last 30 years have shown, in explaning the plasmatic and cellular components of hemostasis, that in close relationship to the vessel wall previously unsuspected mutual exchange reactions directed towards the integrity of the vessel wall exist both in the macro- and the microcirculation. Promoting and inhibiting factors guarantee in a constant, finely balanced interplay with the vessel and its layers the function of the vessel wall as a limiting surface at the beginning of the transit route of the circulation supplying cell and tissue metabolism. Knowledge of the structure and function of transport substances is just as relevant to the physiology and pathophysiology of the vessel wall boundary as the explanation of the nervous and humoral forms of control and their receptor mechanisms. In the pathogenesis of the manifold functional disorders, changes of the hemostatic equilibrium are decisive connecting links for a better understanding, promising new therapeutic formulations. Shock, sepsis, inflammation, organ failure, and tumor metastasis are today just as difficult to understand without the knowledge of hemostasis as is localized vascular damage, up to arteriosclerosis, with all its consequences. Thus hemostasis in the widest sense is an interdisciplinary concern, not only of interest to specialists but also to those involved in theoretical research and clinical activity.

In the present book, F. R. Matthias has successfully organized this field of knowledge. In contrast to many other monographs, he has

concentrated on treating the abundant existing knowledge of the subject. His competence in specialized research (Frerichs-Prize winner of the Deutsche Gesellschaft für Innere Medizin) and his broad clinical experience in the whole field of internal medicine are the most important prerequisites. Well-known facts as well as the most important recent results are brought together, in a mixture which is readily understandable and relevant to practice, to provide a view which gives just as many suggestions to the researcher as to the doctor at the bedside. The recent problems of prostaglandin metabolism and thrombocytes and the vessel wall testify to this just as does modern therapy with fibrinolysis in heart infarct and arterial occlusive disease. I am certain that the book will find a large circle of readers.

Professor H. G. Lasch
Director, Dept. of Internal Medicine
University of Gießen, F. R. G.

Preface

The number of diseases in which the hemostasis system is involved is increasing. This is true for both hemorrhagic diatheses and thromboembolisms. However, this is not true for congenital disorders of the coagulation system and of the thrombocytes. With regard to the increasing morbidity in the population from degenerative cardiovascular diseases in the last decades, coagulation processes and thromboembolic phenomena are an essential partial cause (coronary vascular sclerosis, heart infarct, peripheral arterial occlusive disease, cerebrovascular sclerosis, apoplexy).

The attempt to influence these components in the genesis of the degenerative vascular diseases and prevent thromboembolic complications by using anticoagulants and substances which inhibit thrombocyte function conditions a therapeutically intended defect in the hemostasis system, which can lead to hemorrhagic complications. This is especially true for patients who are receiving additional drugs for other purposes but which have a specific effect on the hemostasis system or a strengthened influence on the therapeutically induced coagulation disorder. Nonsteroidal anti-inflammatory drugs (antirheumatics, analgesics) require mention. Special therapeutic measures require anticoagulation (extracorporeal circulation in heart operations, hemodialysis and hemofiltration in chronic renal insufficiency or intoxications). Every operative intervention which exceeds a certain extent is accompanied by hypercoagulability of the blood, which can lead to thromboses in the deep pelvic-leg vein system, with subsequent pulmonary emboli. The consequences of a post-thrombotic syndrome, which might not develop for a number of years, on a patient's health and on the economy are considerable. Perioperative subcutaneous heparin prophylaxis has brought a clear reduction in the

number of postoperative venous thromboses. In the course of circulatory shock of any origin, in sepsis, in polytraumatised patients, and in polytransfusion coagulation disorders occur which can lead to thrombotic and hemorrhagic complications and which require treatment (disseminated intravascular coagulation, consumption coagulopathy, fibrinolysis).

On these grounds it is necessary for the physician who is active in private practice or in the clinic to be familiar with the pathogenesis of the most frequent disorders of the hemostasis system and to be informed about the measures which are necessary for their correction.

Gießen, 1987 F. Reinhard Matthias

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I. Physiology of Blood Coagulation and Hemostasis

Introduction

The function of hemostasis and of the fibrinolytic systems is the maintenance of the fluidity of the vascular contents and of the integrity of the vessel wall. After local injury of the vascular system the extravasation of blood is stopped by the formation of a hemostatic plug, and after thrombosis a dissolution with total or partial reconstitution of the affected vascular section is attained through the fibrinolytic system. In these processes, vessel wall and vessel contents stand in close interrelationship. The coagulation and fibrinolysis are to be understood as dynamic processes. Many findings support the view that in the blood a constant turnover of coagulatory and fibrinolytic proteins as well as their inhibitors occurs. A physiologically latent coagulation is opposed by a physiologically latent fibrinolysis. Additional conditions are an adequate perfusion of the vascular system and an intact clearance of activated coagulation and fibrinolysis products in the reticuloendothelial system (RES). The processes described are linked to the presence of sufficient and functionally competent hemostasis and fibrinolysis potentials. The actual hemostasis potential results therefore from a balance of a metabolic process, which may be divided into 4 phases:

1. The synthesis of coagulation- and fibrinolysis-active plasma proteins, predominantly in the liver, and of thrombocytes in the bone marrow.
2. The continuous turnover and breakdown of these proteins in the peripheral circulation.

3. The clearance of end products of coagulation and fibrinolysis through the RES.
4. The provision of physiological inhibitors of coagulation and fibrinolysis.

Under physiological conditions the hemostatic equilibrium is maintained in the balance of synthesis, turnover, and degradation of the hemostatic components (eucoagulability). A reduction of the hemostatic potential below a critical level, produces a reduced coagulability of the blood (hypocoagulability), with possible hemorrhagic diathesis as a consequence. An elevation and an activation of coagulation factors lead to overcoagulability of the blood (hypercoagulability) with potential localized or disseminated thrombosis in the vascular system.

Plasmatic Coagulation Factors and Blood Coagulation

Ten glycoproteins are involved in the course of blood coagulation as one part of the hemostatic process (Table 1). They are designated by the Roman numerals I to XIII. Factor III (tissue thromboplastin) is a phospholipid. Factor IV (calcium) and VI (postulated form of activated Factor V) have been omitted.

Table 1. Characteristics of the plasmatic coagulation factors

Coagulation factor	Plasma conc. mg/100 ml	Biological 1/2 life (h)	Hemostatic least conc.	M.W. precursor	Present in serum	Shelf life
I	200–400	96–120	50 mg%	340000	absent	stable
II	10–15	41– 72	40%	72000	trace	stable
V	1	12– 15	10–15%	300000	absent	labile
VII		2– 5	10%	63000	present	stable
VIII	2–5	10– 18	25%	1100000	absent	labile
IX		18– 30	20–25%	55400	present	stable
X	1	20– 42	20%	55000	present	stable
XI		10– 20	15–20%	160000	present	stable
XII	1	50– 70		90000	present	stable
XIII	1–2	100–120	10%	320000	trace (10%)	stable

Factors II, VII, IX, X, XI, and XII are proteases with the amino acid serine in the active centre. They occur in the blood as proenzymes and are transformed in the course of the coagulation process into active enzymes.

Factors V and VIII are not enzymes, but nevertheless are necessary as cofactors at certain points in the coagulation system to ensure a normal course. The last step in coagulation is the enzymatic transformation of fibrinogen to fibrin through the action of thrombin. Factors II, V, VII, IX, XI, and XII as well as prekallikrein and so-called "high molecular weight" kininogens, which both participate in the coagulation and fibrinolysis process, are synthesized in the liver.

The fibrinogen molecule is symmetrically constructed and consists of six polypeptide chains, of which two are always identical (Fig. 1). The three different chains are described as alpha, beta, and gamma. They are linked through disulfide bridges. At the N-terminal ends of the alpha and beta chains are situated the fibrinopeptides A and B, respec-

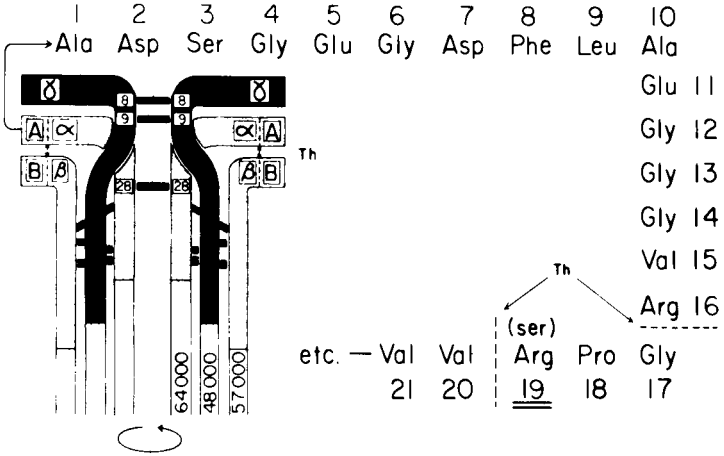

Fig. 1. Schematic presentation of the N-terminal portion of the dimeric fibrinogen molecule. Indicated are the fibrinopeptides A and B, the alpha, beta and gamma chains, the disulfide bridges between positions 8 and 9 of the corresponding gamma chain as well as in position 28 of the alpha chain, the molecular weight of the individual chains, and the amino acid sequence of the terminal end of the alpha chain (fibrino peptide A: amino acids 1–16).
In dysfibrinogen "Detroit" the amino acid in position 19 is replaced by serine.
Th: cleavage site for thrombin

tively. Fibrin formation can be subdivided into the three phases of proteolysis, polymerization, and stabilization of the clot. First the splitting off of fibrinopeptide A by thrombin from the two alpha chains occurs. Through this a conformational change of the molecule is made possible, which makes the fibrinopeptide B of the beta chain accessible to the attack of fibrin. Already after splitting off of the fibrinopeptide A the second, nonenzymatic phase of the polymerization of the fibrin monomer molecule sets in. It is a case of an end-to-end association by noncovalent bonding. After splitting off of fibrinopeptide B there occurs a side-to-side association of the fibrinogen molecules. The clot which results is still soluble, e.g., in higher molarity urea solutions. Through the active Factor XIII the isopeptide bonding between epsilon amino groups of lysine and gamma carboxamide groups of glutamine is produced. The transpeptidation occurs on several sites between two gamma chains and two alpha chains of neighboring fibrin molecules. Ammonia is liberated by the reactions. The fibrin clot is now no longer soluble in urea or diluted acids (Fig. 2).

Factor XIII exists in the plasma as a tetramer, consisting of two identical subunits, which are designated by the letter a, and two further identical peptide chains, which are designated by the letter b. The catalytic center occurs in the a-chain. The enzymatic activation of Factor XIII follows by the splitting off of peptides from the N-terminal region of both a-chains by thrombin and Factor Xa. In the latter case calcium ions are necessary. The loci of biosynthesis of the a-chains are assumed to be hepatocytes, megakaryocytes, spleen, and uterus, whilst the b-chains are synthesised in the hepatocytes.

The synthesis of factors of prothrombin complex (II, VII, IX, X) is vitamin K dependent. Vitamin K_1 (phylloquinone) is of plant origin,

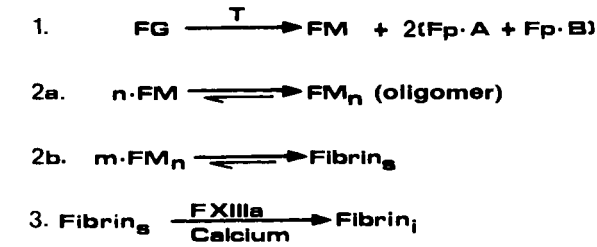

Fig. 2. Fibrin-clot formation. s = soluble; i = insoluble; m and n = unknown whole numbers

and is changed by bacteria in the gastrointestinal tract into vitamin K_2 (menaquinone). The preliminary stage vitamin K_3 (menadione) is transformed in the organism into vitamin K_2. The vitamin K substances are analogues of the 2-methyl-1, 4-naphthoquinones. They possess structural similarities to the coumarin derivatives and the indanediones.

The mechanisms of formation of the factors of the prothrombin complex, especially of prothrombin, have been elucidated (Fig. 3). The prothrombin precursors 1 and 2 are formed independently of vitamin K. In the post ribosomal phase of the synthesis vitamin K as semiquinone or hydroquinone is necessary for the introduction of carboxyl groups into the gamma position of several glutamic acid residues of the prothrombin precursor. By this means prothrombin and the remaining factors of the prothrombin complex are able to bind calcium and to assume relationships to membrane phospholipids. In the activation of prothrombin to thrombin, the protein molecule is split, but the fragments are held together by a disulfide bridge, and fragments 1 and 2 are split off. Thrombin splits off only fragment 1 from prothrombin.

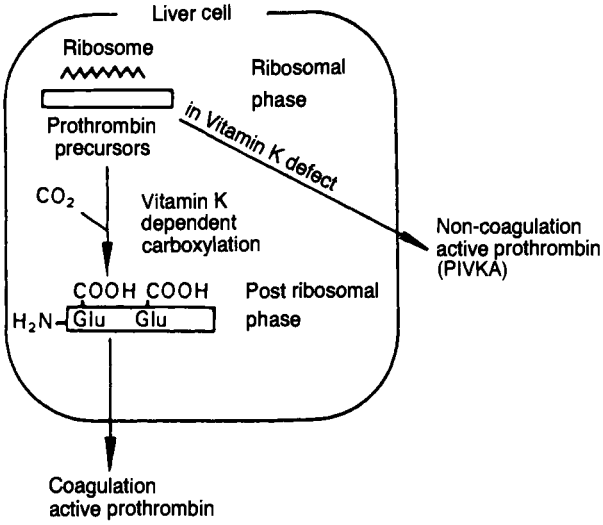

Fig. 3. Prothrombin synthesis and defective prothrombin formation in vitamin K deficiency

This fragment contains the gamma-carboxyglutamic acid which is necessary for calcium binding. In the absence of vitamin K and in the presence of coumarin derivatives the transformation into carboxyprothrombin is omitted. The molecule is released as a functionally ineffective precursor into the circulation. It acts as an anticoagulant and is described as PIVKA (protein induced by vitamin K absence). The oral anticoagulants inhibit the enzymatic transformation of the resulting vitamin K epoxide into vitamin K hydroquinone (Fig. 1/IV). The activated factors of the prothrombin complex (especially Factors Xa and VII a) are resynthesized in the liver to functionally intact coagulation proteins.

The Factor VIII molecule consists of several subunits. A smaller part with a molecular weight of about 200,000 contains the coagulation-active component (Factor $VIII_{coag.}$). The larger part of the molecule with a molecular weight of ca. 1.1 million is demonstrable with heterologous antisera, and carries the von Willebrand Factor activity. The synthesis of the large molecular-weight fraction probably occurs in the vascular endothelium, and the small molecular-weight fraction may also be formed in the endothelium and/or the RES.

The so-called contact factors XII and XI act at the beginning of the activation of the coagulation system. Factor XII represents with its polyvalent activity the connecting link between the systems of coagulation, fibrinolysis, the complement and kallikrein-kinin system.

The coagulation factors are demonstrable in the interstitial fluid as well as in the plasma. About 46% of the total fibrinogen is distributed in the extravascular space.

The course of coagulation is subdivided according to the basic scheme of Morawitz (1905), which is still valid today, into three phases (Fig. 4):

1. The activation of factor X (blood thrombokinase) either by the endogenous (intrinsic) or the exogenous (extrinsic) route.
2. The liberation of thrombin.
3. The formation of fibrin.

The endogenous route corresponds to intravascular coagulation (platelet-plasma system). The exogenous route corresponds to the mechanism in tissue injury, and can be compared with the local coagulation process. Nevertheless, a sharp separation is not admissible,

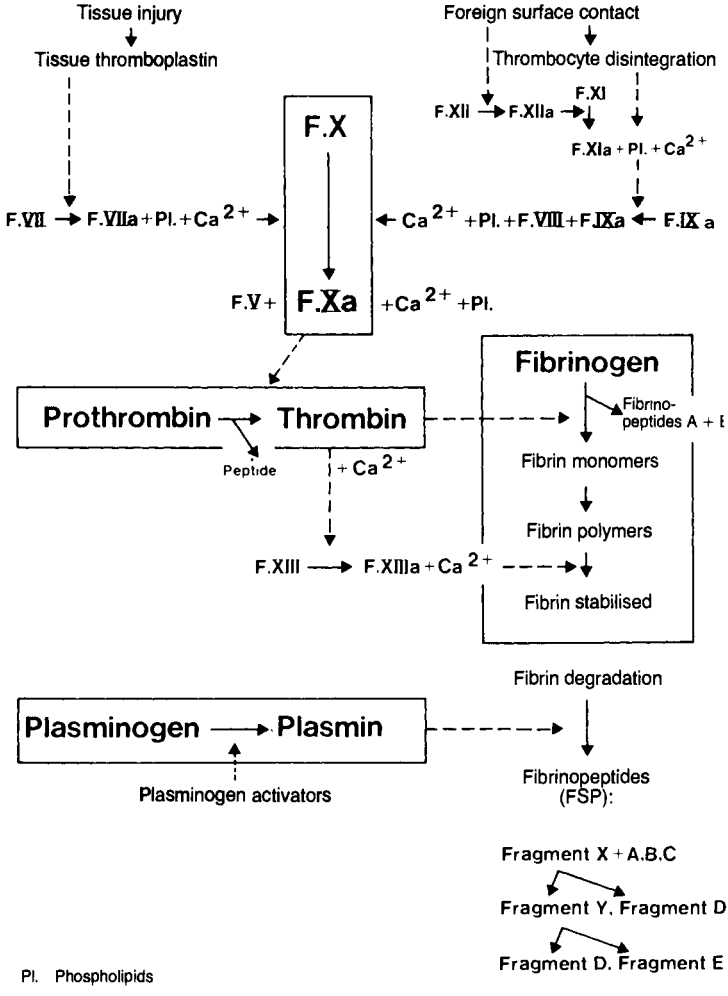

Fig. 4. Blood coagulation and fibrinolysis (From Barthels, Poliwoda 1980, III)

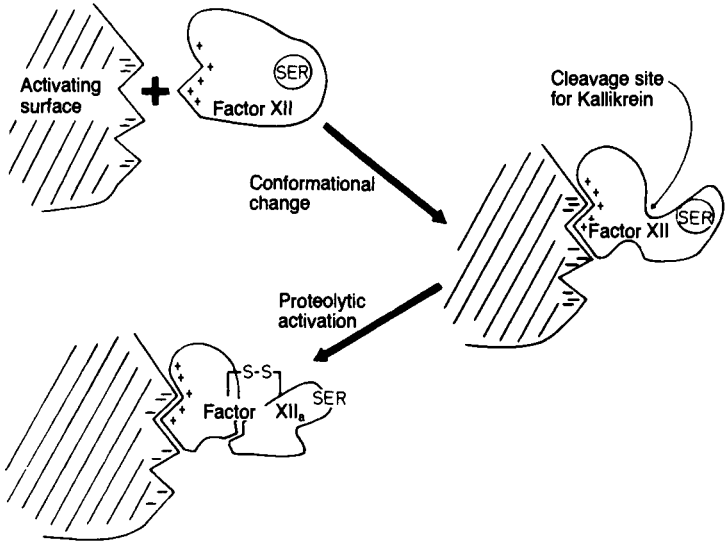

Fig. 5. Conformational changes of factor XII through adsorption on activating surfaces with opening of cleavage site for plasma kallikrein and other proteinases. SER = serine (Griffin 1981)

because various mutual actions between the endogenous and exogenous courses of coagulation exist.

The endogenous route begins with the contact activation of Factor XII. Inactive Factor XII (molecular weight 80,000) becomes bound to negatively charged activating surfaces (Figs. 5 and 6). These can be damaged vascular endothelium, basal membranes, collagen, or platelet lipids. Simultaneously Factor XI, high molecular weight (HMW) kininogen, and prekallikrein are bound.

The inactive Factor XII undergoes a conformational change of its molecular structure through surface contact, which make possible the formation of Factor XII a-alpha through splitting of a peptide bond. Factor XII a-alpha consists of two polypeptide chains with molecular weights of 52,000 and 28,000 respectively, which are held together by a disulfide bridge. The heavy chain contains the binding area, the light

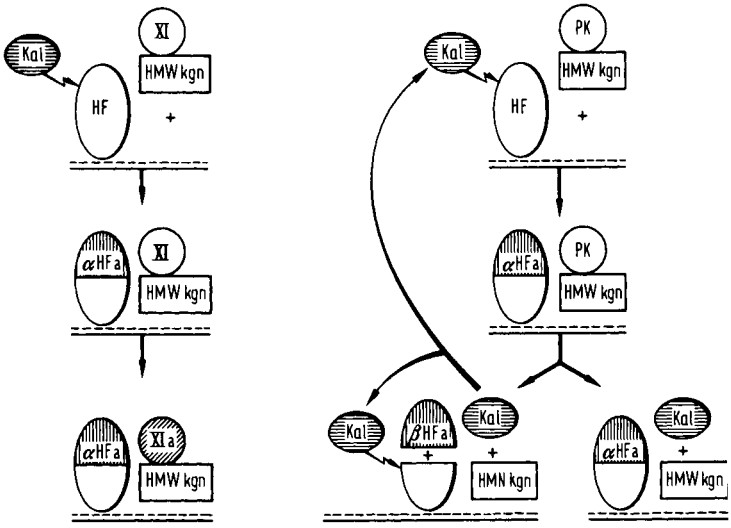

Fig. 6. Demonstration of surface-dependent arrangement of the molecules answerable for the contact activation reactions. PK = pre kallikrein; Kal = kallikrein; HMW kgn = HMW kininogen; HF = Hageman Factor (Factor XII) (Griffin 1981)

chain the active center. Through further proteolysis Factor XII a-beta arises, which consists of the light chain and a small part of the heavy chain. Factor XII a-beta can no longer bind to a surface, and is released into the plasma. However, it possesses enzymatic activity. Factor XII a-alpha changes pre-kallikrein into kallikrein and activates Factor XI. The same process occurs bound to surfaces. Only the presence of HMW kininogen makes this process possible. Kallikrein and Factor XI a activate further Factor XII by a positive feed-back mechanism. The Factor IX actived by Factor XI a forms a complex with Factor VIII, calcium ions, phospholipids and Factor X. The phospholipids (phosphatidylcholine and phosphatidylethanolamine) are made available from the thrombocytes and are named Platelet Factor 3. Factor VIII has the function of a reaction accelerating cofactor.

The exogenous route of coagulation is started through liberation of tissue thromboplastin after injury of endothelial cells and tissues.

Thromboplastin is a lipoprotein which forms a complex with Factor VII and calcium ions. In this complex, in which Factor VII now exists in an activated state, Factor X is taken up and activated to Factor Xa (blood thrombokinase). Henceforth the route of the extrinsic and intrinsic systems is identical. Factor Xa forms a complex with Platelet Factor 3, calcium ions, Factor V which functions as the reaction-accelerating cofactor, and prothrombin. In this compound prothrombin is transformed by the serine protease Factor Xa to thrombin. Thrombin has several functions: it changes fibrinogen into fibrin, activates the fibrin-stabilizing Factor XIII, increases the activity-readiness of Factors V and VIII, activates thrombocytes and causes the aggregation, viscous metamorphosis, and disintegration of thrombocytes, causes a partial proteolysis of prothrombin, and stimulates prostacyclin formation in the endothelial cells.
Numerous experimentally demonstrable reciprocal interactions between the extrinsic and intrinsic systems exist. Thus Factors XIIa, XIa, and Xa can directly activate Factor VII. Factor VII transforms Factor IX into Factor IXa. This has the consequence that in the course of coagulation the intrinsic and extrinsic systems are simultaneously set in motion, to a varying extent on each occasion.

Fibrinolysis System

The key enzyme in fibrinolysis is the serine protease plasmin (Fig. 7). It arises through limited proteolysis from plasminogen. Plasminogen has a molecular weight of 91,000 and a plasma half-life of 2–2.5 days. The N-terminal amino acid is glutamine. By splitting-off of a peptide by traces of plasmin he so-called Lys-plasminogen occurs, which has lysine as its terminal amino-acid. Lys-plasminogen has a stronger affinity for fibrin than Glu-plasminogen, and can be transformed more easily by the activators into plasmin. Plasminogen is formed in the liver. An intrinsic and extrinsic route can also be differentiated in the transformation of plasminogen to plasmin. The intrinsic transformation results from a blood activator, Factor XIIa and also kallikrein. In the extrinsic route a vascular wall activator, a tissue activator, or urokinase are liberated, which convert plasminogen into plasmin. How they are liberated from vascular endothelium and tissues is largely unclear. Besides hypoxic or other kinds of damage of the

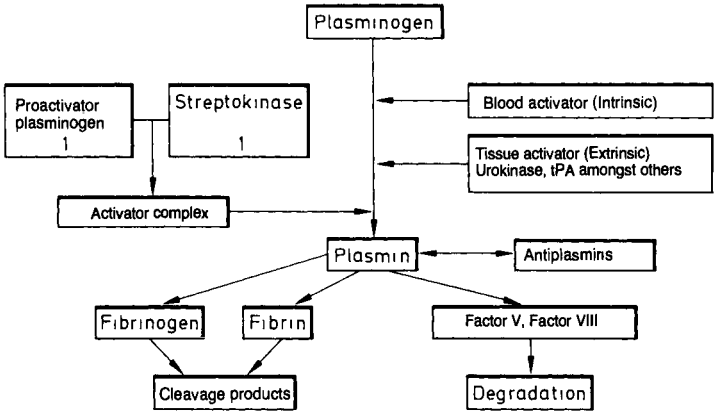

Fig. 7. Transformation of plasminogen into plasmin and plasmin action

vascular wall, the action of thrombin and fibrin precipitated on the vascular wall can also play a part. This would give a plausible explanation for the local activation of fibrinolysis, bearing in mind the fact that plasminogen and the activators on lysine binding sites have a high affinity for fibrin. The plasminogen molecule functions as a proactivator and as a proenzyme. It binds itself in a stoichiometric proportion of 1:1 with streptokinase and thus becomes an activator complex, which can activate further plasminogen molecules. Here lies a decisive difference between therapeutic fibrinolysis treatment with streptokinase and urokinase. Whereas urokinase can form plasmin directly, streptokinase induces a conformational change of the plasminogen molecule. In this way they become enzymatically active and can then in the activator complex transform further plasminogen molecules into plasmin. The endothelium of venules, the uterus, suprarenals, prostate, thyroid, lung, lymph nodes and meninges are especially rich in tissue activators. Brain contains little and liver tissue no activator. Leukocytes also possess activators, which can have great pathophysiological significance.

Plasmin degrades enzymatically both fibrinogen and fibrin (Figs. 7 and 8). In the course of fibrino(gen)olysis initially fragment X (molecular weight 250,000) occurs: through splitting off of a fragment D (molecular weight 80–100,000) fragment Y (molecular weight ca. 150,000) is formed. Fragment Y decomposes finally into a further Fragment D and a Fragment E (molecular weight 50,000). Whereas Fragment X is

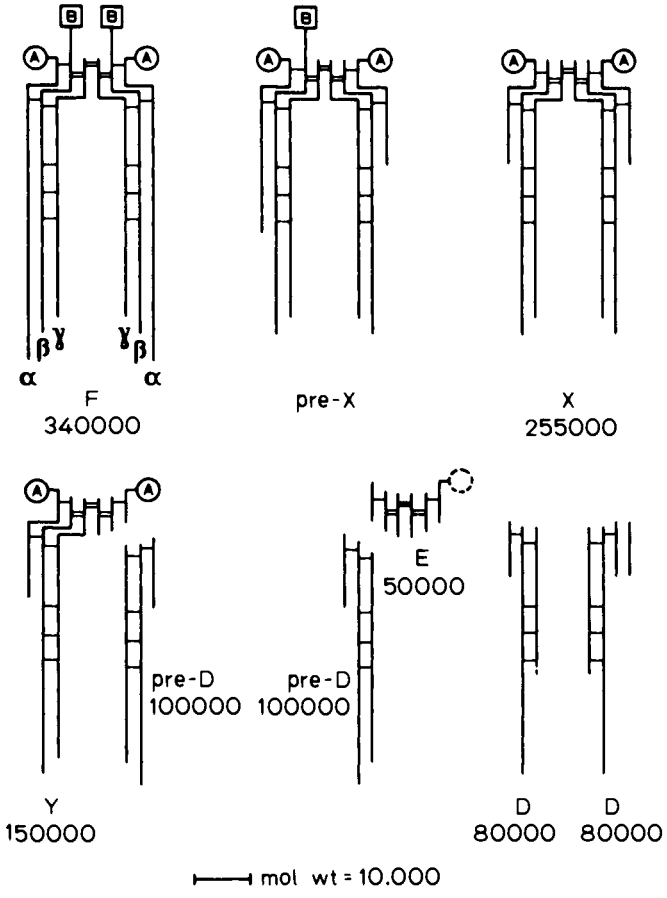

Fig. 8. Plasmin-induced degradation of fibrinogen into cleavage products X, Y, D and E. A, B = Fibrinopeptide; alpha, beta, and gamma = chains of the fibrinogen molecule (Kopeč, Latallo 1978)

still coagulable, the rest of the fragments are no longer so. However, because there are still polymerization centers available in a residue, they interfere with the fibrin polymerization and delay or prevent fibrin clot formation in extreme cases. Fragment E has an antithrombin effect. The cleavage products therefore have an anticoagulant action which is responsible for the prolongation of the thrombin and reptilase times. Beyond that plasmin destroys Factors V, and VIII, and also prothrombin. The numerous reciprocal relationships between the coagulation and fibrinolysis systems are obvious.

Inhibitors of Coagulation and Fibrinolysis

In the plasma numerous anti serine proteases are present (Table 2). They inhibit to different extents plasmin or plasminogen activation and the enzymes of coagulation systems. Most important are the alpha$_2$-antiplasmin and antithrombin III. Alpha$_2$-antiplasmin is a glycoprotein with a molecular weight of 70,000, a plasma concentration of 5–7 mg% and a plasma half-life of 2.3–2.9 days. It is synthesized in the liver. Alpha$_2$-antiplasmin forms a very stable 1:1 stoichiometric complex with plasmin, which in this way loses its protease activity. Plasmin, in which through binding of 6-aminohexanoic acid, the lysine binding sites are blocked, and/or substrate is bound to the active center, reacts badly with alpha$_2$-antiplasmin. In primary plasminogen-plasmin transformation the alpha$_2$-antiplasmin therefore binds very rapidly to the resulting plasmin, and protects circulating fibrinogen from the proteolytic action of the enzyme. If in thrombogenesis plasminogen is bound to the lysine binding sites on precipitating fibrin and secondarily activated, the plasmin arising is extensively withdrawn from the access of antiplasmin, and can develop its proteolytic action. In fibrinolysis alpha$_2$-antiplasmin is consumed.

Antithrombin III is a polyvalent inhibitor of serine proteases. The coagulation factors IIa (thrombin), IXa, Xa, XIa, XIIa, plasmin, and kallikrein, as well as C1 of the complement system are inhibited. The binding of the antithrombin III to the activated proteases occurs very slowly. One can assume that under *in vivo* conditions the activated proteases first interact with their substrate, before an inhibition can result. The binding rate of antithrombin III to thrombin and the other proteases and their inhibition can be considerably increased by hepa-

Table 2. Protease inhibitors and their action in the hemostasis system

Inhibitor	M.W.	Plasma conc.	Conc. µMol/l	Biological 1/2 life	Disease with cong. defect	Possible essential importance
α_1-Antitrypsin	54000	130–250 mg/dl	45.0	4 days	lung emphysema	Trypsin inhibitor
α_1-Antichymotrypsin	69000	30– 60 mg/dl	7.0			Chymotrypsin inhibitor
Inter-α-Trypsin-Inh.	160000	20– 70 mg/dl	3.1			Trypsin inhibitor
Antithrombin III	65000	14– 20 mg/dl[+] 22– 39 mg/dl 85–125%	4.5	ca. 2½ days	Thrombophilia	Progressive antithrombin after complex formation with heparin Immediate antithrombin
$\overline{C1}$-inactivator	104000	15– 35 mg/dl	2.3	38–40 h	Hereditary angioneurotic edema (HANE)	Activation control of coagulation, fibrinolysis, kallikrein, and complement system
α_2-antiplasmin	70000	6– 10 mg/dl	1.0	2.5 days	Miyasato syndrome	Immediate antiplasmin
α_2-macroglobulin	725000	150–350 mg/dl ♂ 175–410 mg/dl ♀	3.3	10 days	No symptoms	Polyvalent inhibitor Progressive antiplasmin

[+] Depending on the method

rin. Different theories have been put forward on the mechanism of action. It is probable that the serine protease forms a complex with heparin and antithrombin III, whereby heparin accelerates the binding of antithrombin III to the protease. Heparin is then liberated from the further inactivated complex, and can again display its action. Antithrombin III is on a weight basis 30 times more active against Factor Xa than against thrombin. Through this the antithrombotic effect of the so-called "low dose" heparin prophylaxis is understandable. It is begun before a possible activation of the coagulation system (e.g., peri operative), before Factor Xa and thrombin are produced. If an activation of the coagulation with formation of Factor Xa occurs, in the presence of antithrombin III a small amount of heparin suffices for its inactivation. Prothrombin inactivation is then theoretically no longer possible.

The remaining protease inhibitors display their action with different intensity in the coagulation and fibrinolysis systems and modification of their course. However, they seem to come behind the two above-mentioned inhibitors in their effectiveness.

The course of coagulation is inhibited by other mechanisms. Factor Xa first activates Factor VII and then destroys its activity. Likewise, thrombin initially promotes the activities of Factors V and VIII and then inactivates them. The recently discovered so-called protein C, vitamin K-dependent in its synthesis, is transformed into an active protease by thrombin, and inhibits coagulation by degradation of Factors V and VIII. The activation of protein C in the plasma takes place slowly. There is over 1000-fold acceleration of the activation at the endothelial cell surfaces. Thrombomodulin acts as cofactor localized at the endothelial cell. Thrombomodulin binds thrombin, which thereby loses its procoagulatory activity. The thrombomodulin/thrombin complex binds protein C. In this complex protein C is converted from its inactive into its active form by thrombin with a high turnover rate. Protein S acts as cofactor for activated protein C in the inactivation of Factors Va and VIIIa (Fig. 9). Fibrin adsorbs thrombin. Fibrin cleavage products inhibit fibrin polymerization.

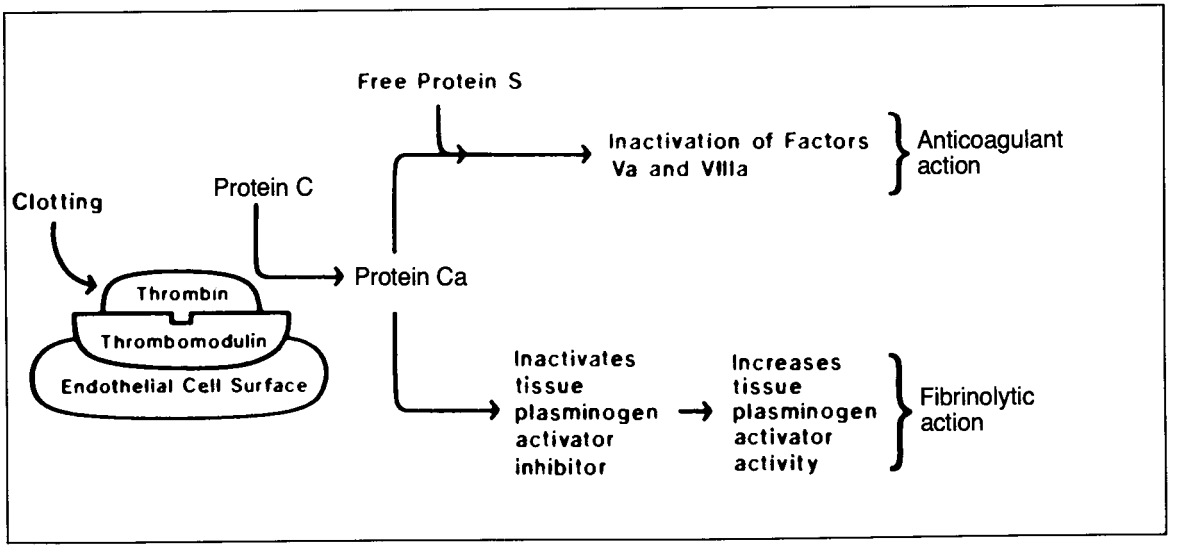

Fig. 9. Thrombin-thrombomodulin model of the anticoagulant and fibrinolytic action of Protein C

Relationships Between Coagulation, Fibrinolysis, Complement and Kallikrein-Kinin Systems

Numerous correlations between coagulation and fibrinolysis systems have been repeatedly pointed out (Figs. 9 and 10). The activated Hageman Factor (Factor XIIa-alpha and Factor XIIa-beta) takes a central position. It starts the coagulation course in the intrinsic system and can also directly activate Factor VII. It is concerned with the transformation of plasminogen proactivator into activator for plasmin formation. It transforms pre kallikrein into kallikrein and activates the complement system. Plasmin again influences the three remaining systems. Kallikrein activates Factor XII, supported by kininogen. The entire system is stabilized by numerous inhibitors, whereby significant functions are allotted to the C 1-inactivator and the $alpha_2$-macroglobulin besides the anti thrombin III. These systems are involved in close inter-relationship in inflammatory and immunological processes. Thrombin-activated protein C inactivates not only the coagulation Factors Va and VIIIa, but also neutralizes the inhibitor of the tissue plasminogen activator (tPA) as well. Protein C thus intervenes in a regulatory way in the fibrinolysis system. Protein S circulates in the plasma in free form, in which it acts as cofactor to protein C. Protein S is also present in a high molecular weight form bound to C4b binding protein. The C4b-binding protein is an inhibitor of the complement system. In this way the protein S influences the local regulation of the complement system at phospholipid surfaces.

Reticuloendothelial System (RES)

Circulating end-products of coagulation and fibrinolysis are eliminated from the vascular system by the reticuloendothelial system. Depending on perfusion and functional condition, a circulatory and a phagocytic clearance capacity of the RES are distinguished. The Kupffer's cells of the liver comprise over half of the clearance capacity of the RES. The lung also possesses a high clearance capacity for activated coagulation products. Of the procoagulatory active substances, especially thromboplastin, fibrin monomer, and cellular fragments with procoagulatory activity as well as fibrinolysis activators, high molecular-weight cleavage products, thrombin-antithrombin III and plasmin-

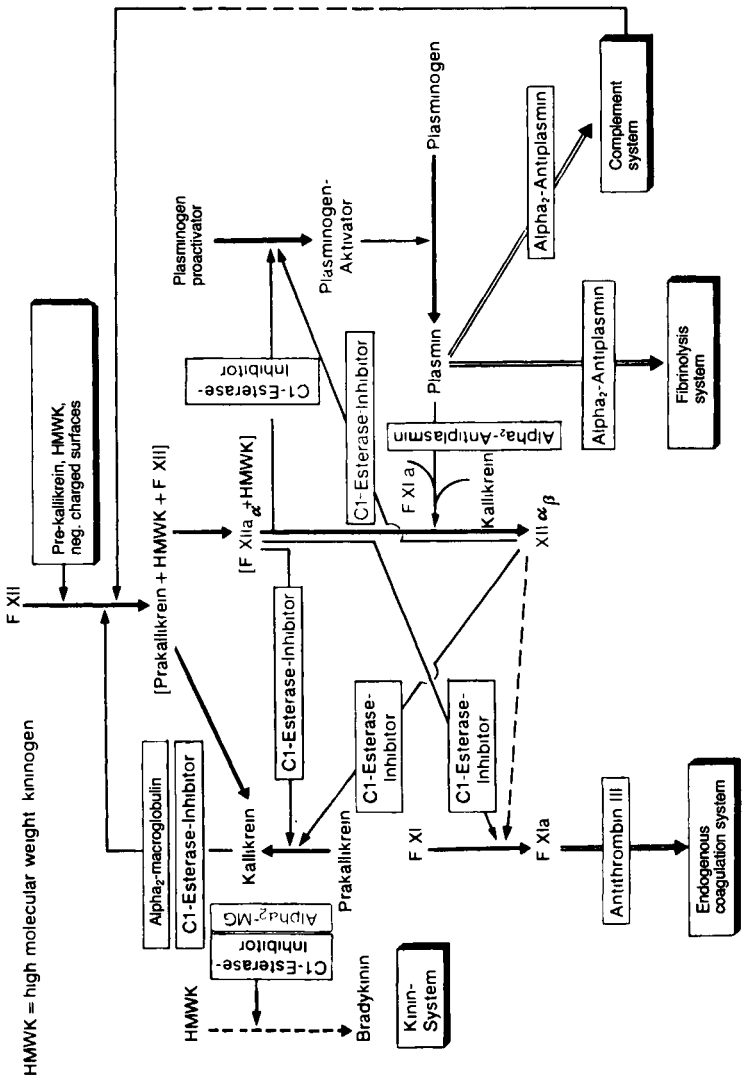

Fig. 10. Relationship between coagulation, fibrinolysis, complement, and kallikrein-kinin systems

alpha$_2$-antiplasmin complexes are cleared from the circulating blood. The phagocytotic function of the RES is inhibited by numerous factors (pregnancy, circulatory shock), through which an increased tendency to thrombosis arises due to reduced phagocytotic capacity. Monocytes and macrophages are able to express thromboplastic activities at their surface and also to release plasminogen and plasminogen activators. The RES thus intervenes directly in the process of coagulation and fibrinolysis.

Thrombocytes

The thrombocytes arise from the cytoplasm of the megakaryocytes (Fig. 11). They have a longitudinal diameter of 2–4 μ and a transverse diameter of 1 μ. The thrombocyte count in the peripheral blood lies between 150,000 and 300,000/mm^3. The platelet survival time amounts to 7–11 days. The cytoplasm of the resting thrombocytes is enclosed in a glycoprotein casing, which exhibits various kinds of invaginations into the cytoplasm; these are called a "surface-connected open canalicular system". In the intermediary zone (sol-gel zone) an annular bundle of microtubules is present, as well as microfilaments of an

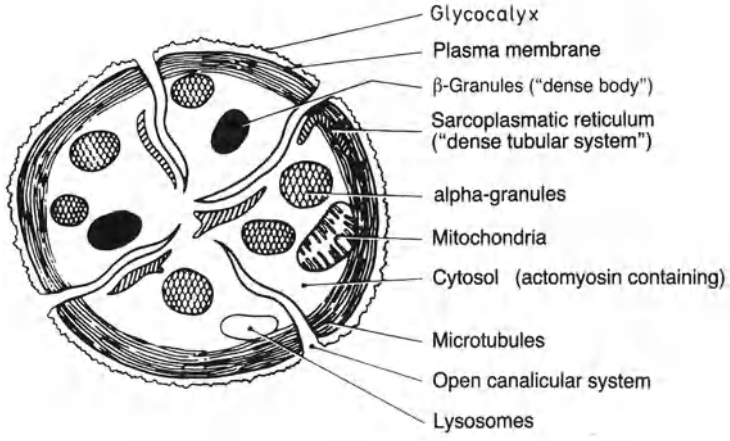

Fig. 11. Morphology and structure of a thrombocyte

actomyosinlike contractile protein, thrombosthenin. The microtubules stabilize the exterior form of the resting platelets. The thrombocytes show a series of storage granules. The alpha granules contain fibrinogen, platelet growth factor (PDGF = platelet derived growth factor), platelet factor 4, beta-thromboglobulin; the beta granules ("dense bodies") contain the metabolically inactive ADP and serotonin. The lambda granules contain lysosomal enzymes. The so-called "dense tubular system" consists of a membrane system of canals and vesicles. It is supposed to be analogous to the sarcoplasmic reticulum of muscles and is a site of calcium storage. In this system there is a part of the prostaglandin and thromboxane storage system. After an excitatory stimulus the thrombocytes are adapted to the following morphological and functional changes (Fig. 12): adhesion, shape change, aggregation, secretion ("release reaction"). The initial event in the formation of a platelet thrombus is platelet adhesion at the site of vascular injuries. The binding of Factor VIII/von Willebrand Factor to the subendothelium promotes adhesion, and is followed by shape change, which can also be observed *in vitro* in the aggregometer

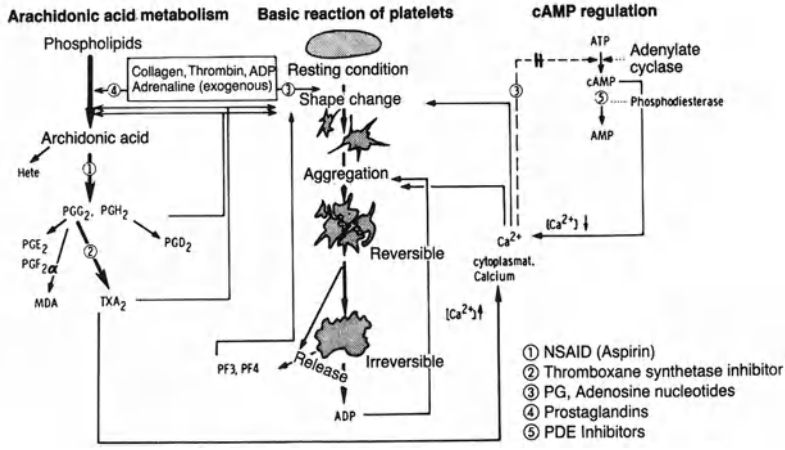

Fig. 12. Thrombocyte aggregation system after stimulation and the most important intrathrombocytic biochemical reactions during the course of aggregation, and their interactions (Reuter 1981, XIV)

after the addition of platelet stimulating substances. Thrombin, collagen, subendothelial tissue, immune complexes, ADP, adrenaline, noradrenaline, serotonin and vasopressin are platelet-activating substances.

The transformation of the disk form to the spherical form proceeds with the formation of pseudopodia, which become adherent to the vessel wall structures. The process is reversible. With sufficiently intense platelet stimulation a deposition, also reversible, of numerous platelets occurs – the aggregation. In the aggregometer this phenomenon is represented by the so-called first phase of aggregation. With sufficiently strong stimulation the second phase of aggregation follows. A pre-requisite for the regular course of this phase is the accompanying release reaction, with liberation of the substances within the granules. This degranulation occurs after a preceding centrally directed deposition of the organelles, and is accompanied by polymerization of the cytoplasmic thrombosthenin. The "release reaction" promotes the aggregation of further thrombocytes. The process of aggregation is calcium-dependent. Whereas thrombocytes can be brought to aggregation by minimal quantities of thrombin, which are still insufficient for clot formation, the aggregation-triggering concentration of adrenaline *in vivo* is not attained; nevertheless adrenaline has an aggregation promoting action. Fibrinogen does not react with unstimulated thrombocytes. After activation, however, receptors are exposed to bind the fibrinogen and fibrin, and to form bridges between the thrombocytes. Lower concentrations of activators lead to a secretion of the contents of the alpha granules, higher to one of beta-granules; substances of the lambda granules are finally liberated. A degranulation can also occur without aggregation of thrombocytes.

Three metabolic routes are postulated which can have aggregation as a consequence. For the first it is assumed that ADP after stimulation of the thrombocytes takes over a mediator function. During the aggregation ADP is released, and leads to aggregation of further thrombocytes. An alternative route to aggregation runs through the prostaglandin-thromboxane system (Fig. 13). From the thrombocyte membrane arachidonic acid is liberated by phospholipase A_2 or a diglyceride lipase. The phospholipase is stimulable by calcium ions. The arachidonic acid is transformed through cyclo-oxygenase and oxygen uptake into the prostaglandin derivatives PGG_2 and PGH_2. In a further step the transformation into thromboxane A_2 results from the

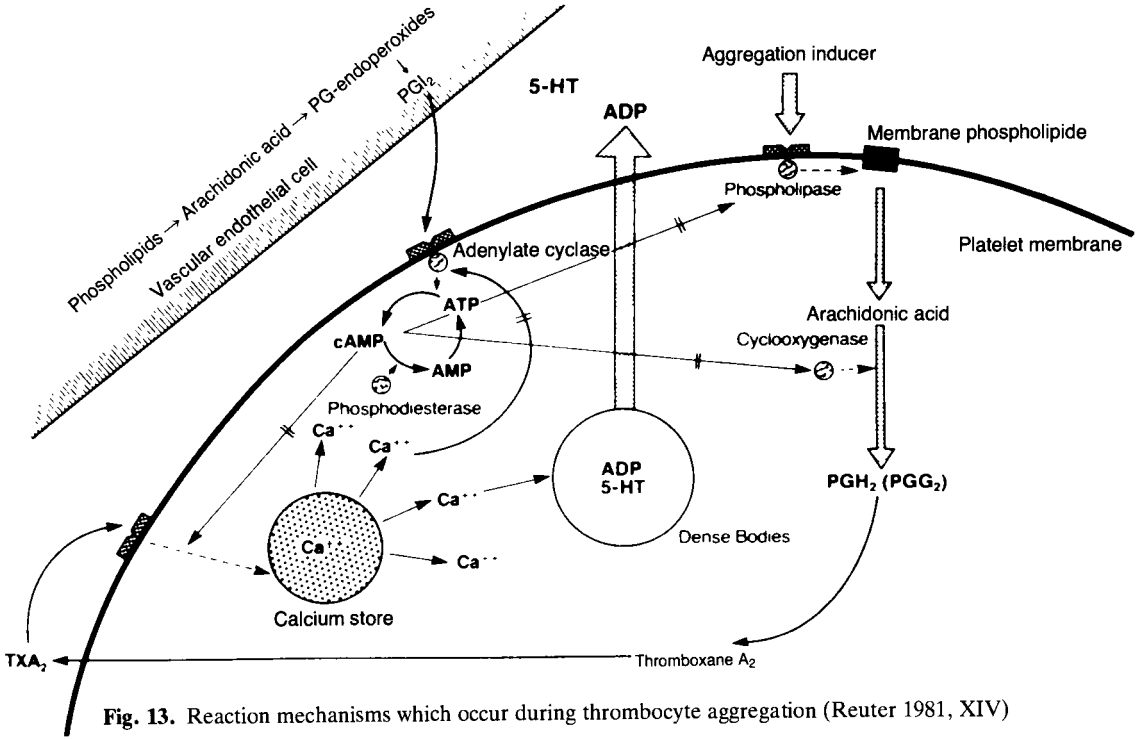

Fig. 13. Reaction mechanisms which occur during thrombocyte aggregation (Reuter 1981, XIV)

action of thromboxane synthetase. Besides these, further prostaglandin derivatives occur in the thrombocytes in small quantities with in part aggregation-inhibitory actions (PGD_2, PGE_2, $PGF_{2\alpha}$). Thromboxane A_2 has a half-life of 32 sec., and has a powerful aggregation-promoting and vasoconstrictor action. Whereas phospholipase A_2 liberates arachidonic acid from phosphatidyl choline, which is localized on the outer side of the platelet membrane, phospholipase C first liberates inositol phosphate from phosphatidyl inositol, on the inner side of the membrane. The diglyceride lipase then splits arachidonic acid from the second C atom of the glycerol. It remains an open question which liberation mechanism is decisively involved in the liberation of arachidonic acid *in vivo*. Calcium translocations play an essential role. Thromboxane A_2 decrease the concentration of cyclic 3′5′-AMP in the thrombocytes. Cyclic 3′5′-AMP inhibits phospholipase A_2. Substances which lead to the stimulation of the membrane bound adenylcyclase, for example prostacyclin, induce a cyclic AMP increase and inhibit the phospholipase and thrombocyte aggregation. A third route to platelet aggregation after stimulation is mediated by the so-called platelet aggregating factor (PAF). It involves the phospholipid 1-O-alkyl-2-O-acetyl-2-*sn*-glyceryl-3-phosphorylcholine, arising from lysolecithin through acetylation. The platelet aggregating factor also arises in thrombocytes in numerous cells. The mechanism of liberation of PAF is at present unknown. Calcium ions are again essentially concerned.

The aggregation routes mentioned depend to differing extents on the form and intensity of the stimulus. Thus for complete aggregation with low concentrations of ADP and thrombin the activation of the prostaglandin-thromboxane system is necessary. With large amounts of thrombin and collagen a marked aggregation is obtained after inhibition of cyclo-oxygenase, e. g., with acetyl salicylic acid.

Vessel Wall, Thrombocytes, and the Coagulation System

The intact vascular endothelium does not react with thrombocytes or other blood components. This is probably in part due to the repulsive power of similar types of electrical charges on the vascular endothelium and thrombocytes. Endothelial cells with functional

capacity produce prostacyclin on stimulation, e.g., after contact with thrombin traces and activated platelets, which as a potent anti-aggregatory substance can inhibit or limit the formation of platelet aggregates. The endothelium-fixed ectonucleotidase changes ADP, which is liberated from a platelet aggregate and would promote the deposition of further thrombocytes, into adenosine monophosphate (AMP) and adenosine. In what way these mechanisms can be active in the blood stream is not completely explained. Whether the prostaglan-

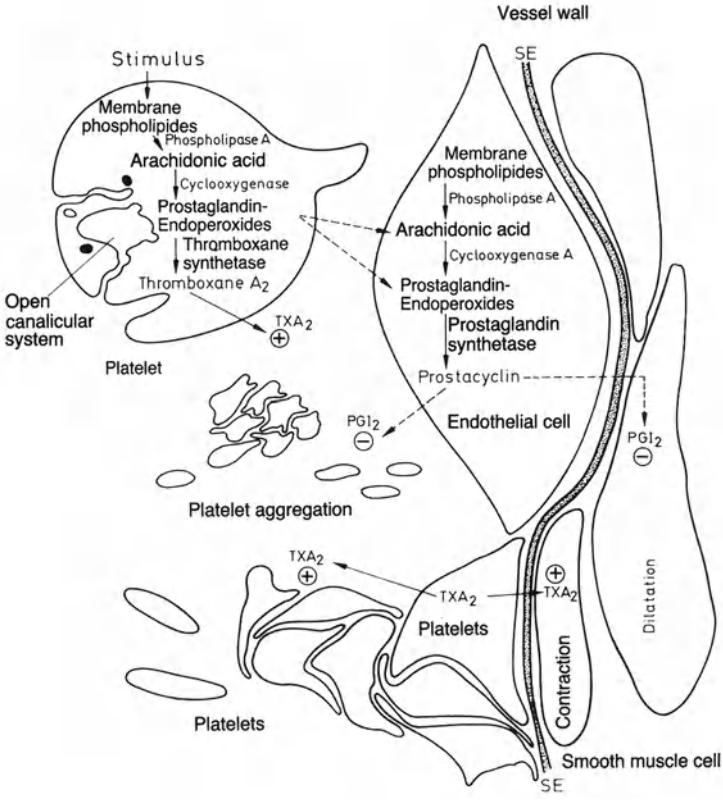

Fig. 14. Interaction between thrombocytes and vessel wall with particular reference to thromboxan A2 and prostacyclin. + positive influence; – negative influence; SE = subendothelium (Barnhart, Chen 1978)

din endoperoxides formed in stimulated thrombocytes, in close spatial contact to the endothelial cells, can diffuse, and there be transformed into prostacyclin, which has been postulated on the grounds of *in vitro* experiments, seems at least questionable (Fig. 14). The platelets probably become adherent to damaged endothelial cells (Fig. 15). They stick to collagen, basal membrane structures, and microfibrillae of subendothelial tissues. The interaction is supported by the von Willebrand Factor, which is synthesized in the endothelial cells. The "release reaction" is induced by fibrillar collagen; on the endothelium and subendothelial tissue adsorbed thrombin traces have a supporting action. During the activation of thrombocytes and aggregate formation phospholipids of membrane origin are made available; these are necessary for the regular course of the coagulation system. Membrane components can serve as activating surfaces for Factor XII. A direct activation of Factor XI should also be possible. Although the participation of thrombocytes in an assumed transformation of Factor IX into Factor Xa is not fully explained, it should involve a complex formation between Factor IXa, platelet phospholipids, Factor VIII,

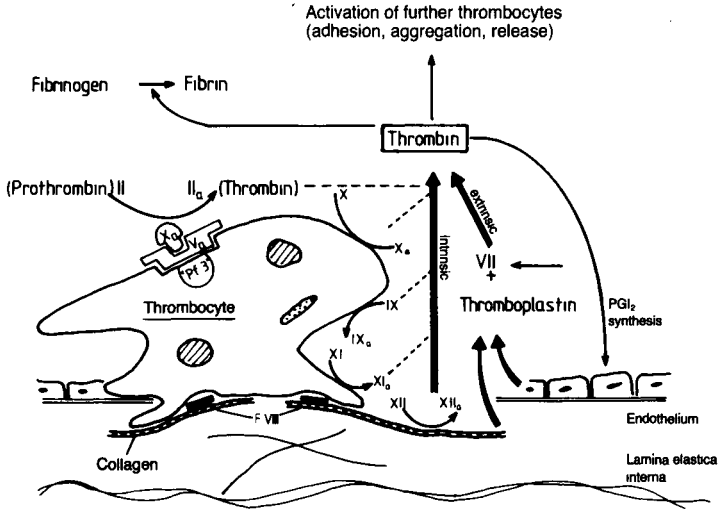

Fig. 15. Functional relationships between thrombocytes, plasmatic coagulation system, and damaged vessel wall (Reimers 1981, II)

Factor X and calcium, with consecutive activation of Factor X. Binding of Factor V to platelet phospholipids has been observed. In a complex forming with collagen and Factor X the transformation into Factor Xa follows, whereby the end section of the coagulation cascade is attained and would have started. The thrombin that arises acts as a positive feedback mechanism back-reacting with platelet aggregate formation, in which it leads to ADP liberation, the formation of thromboxane A_2, and the availability of platelet aggregating factor (PAF).

Fibrinogen from plasma or thrombocytes is necessary for the sticking of thrombocytes to one another. Fibrin has an aggregation promoting effect. After endothelial injury tissue thromboplastin is liberated, which with Factor VII contributes to further formation of thrombin through the extrinsic system.

Hemodynamic factors have a decisive influence on the interaction of blood cells, especially of thrombocytes, and vascular walls. With linear flow the cells flow in the main current in which the erythrocytes occur centrally. The flow of the corpuscular particles is covered by a plasmatic mantle, which impedes the interaction between the vessel wall and thrombocytes. It is assumed that there are electrical potentials in vessels, that they originate in vascular lesions, and further that they give the thrombocytes an impulse directed at the vessel walls, and can initiate platelet adhesion. The chemical stimulators must be active in the second line only. In regions of slow flow with low shear stress the aggregate formation on endothelial surfaces is rather small. With increasing shear stress, and increased numbers of platelet collisions, platelet thrombus formation increases. Flow dynamic phenomena play a role in the differing thrombus structure of the venous and arterial limbs of the vascular system. In zones of turbulent flow and in regions behind large mural thrombi the flow can give rise to areas of circulating or stagnant blood where activated thrombocytes and clotting factors can accumulate.

Hemostasis

From the anatomical viewpoint arterial, venous and capillary hemorrhage can be differentiated. A sufficient hemostatic potential is a prerequisite for an adequate control of hemorrhage.

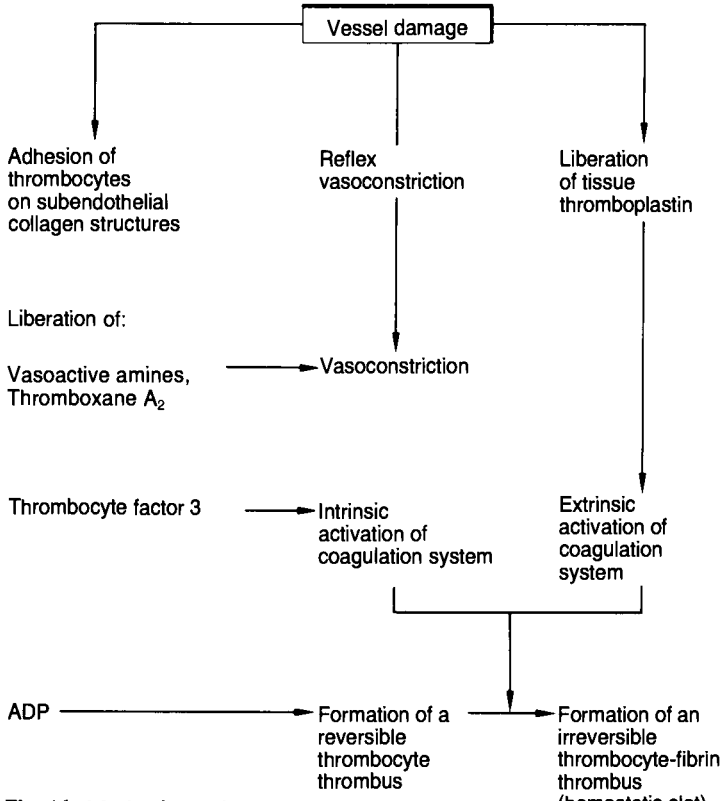

Fig. 16. Mechanisms of hemostasis

A mild hemostatic disorder with moderate lowering of one or some coagulation factors can be compensated without manifest hemorrhagic diathesis occurring.

Hemorrhages from capillaries stop mainly by compression and agglutination of the endothelial cells. With injuries of the arterial and venous vessels the hemostatic process progresses in several phases (Fig. 16):

1. Vascular lesion or endothelial damage with reflex vascular constriction.
2. Adhesion of thrombocytes to exposed subendothelial tissue, collagen and pervascular structures.

3. Aggregation and accompanying liberation of vasoactive and aggregation promoting substances with formation of a loose, locally fixed reversible platelet thrombus.
4. Activation of the coagulation system over the endogenous route through contact activation on altered surfaces and stimulated thrombocytes in relation to tissue and platelet phospholipids; simultaneous activation of the clotting mechanism over the exogenous route after liberation of tissue thromboplastin from damaged cells.
5. Formation of a platelet-fibrin thrombus with thrombus retraction and formation of a reversible hemostatic clot.
6. Fibrin stabilization through Factor XIIIa.

The formation of a hemostatic clot is also a prerequisite for the regular course of the subsequent reparative process of the vascular wall and the wound healing. The fibroblast growth is ensured by the presence of stabilized cross-linked fibrin structure through Factor $XIII_a$ and fibronectin. The fibrinolysis system intervenes in regulating the process of thrombus formation since it limits the thrombus to the site of injury, and any excessive clot formation is broken down by fibrinolysis.

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II. Thrombosis

Introduction

Thrombosis represents the end of an acute or delayed intravascular clotting process that blocks the vascular volume either partly or completely. The extent of the flow obstruction in the affected vessel section determines how far this is manifested in ischemia in the arterial branch of the vascular system and blood stasis in the veins. In both cases, the peripheral vascular regions show altered blood flow, and there may be trophic disorders and tissue injury depending on the extent of the thrombosis.

The term embolism is applied to thrombus material breaking away from the clot and subsequently lodging in remote vascular areas. In venous thrombosis, the embolus lodges in the pulmonary arterial vascular system. Paradoxical embolism occurs when thrombotic material is transported through the apertures between the right and left parts of the heart into the arterial system. Arterial embolism arises from the pulmonary veins, the heart, or the aorta. It results in the obstruction of a peripheral arterial vessel. In a figurative sense, thrombosis can be seen as hemostasis in the wrong place.

Virchow (1856) described the preconditions for a thrombus to develop (Table 1), which still apply:

1. lesions of the vascular wall
2. changes in blood flow behavior
3. changes in vascular content.

The three pathogenetic mechanisms occur to different extents in the veins and arteries. In the initiation of disseminated thrombosis in

Table 1. Pathogenetic factors in venous thrombosis (Virchow's triad)

I. Vascular wall damage

A. Endothelial lesions due to:
Hypoxia
Endotoxins (infections), drug toxicity, allergic reactions, and mechanical stress (turbulence, trauma)
Depletion in fibrinolytic activator (diabetes mellitus)

II. Circulation disorders

A. Venous congestion and stasis
1. Systemic:
Cardiac insufficiency
Obesity
Pregnancy
Immobilization
2. Local:
Organized thrombi (postthrombotic syndrome)
Varicose veins and chronic venous insufficiency
Compression (hematoma, operation wounds, tumors, lymphomas)

III. Changes in vascular content

A. Hypercoagulability due to:
1. Flooding with thromboplastin
a) due to major operations (lung, pancreas, colon, prostate, musculature)
b) following fractures (fat embolism syndrome), soft tissue injury (hemolysis), and burns
c) due to metastatic tumor tissue
2. Fibrinolysis inhibition (diabetes mellitus, lipid metabolism disorders, corticoid therapy, contraceptives, antifibrinolytics)
3. Reduction in the RES clearance capacity (endotoxins, antigen-antibody complexes, thromboplastins, soluble fibrin)
4. Reduction in antithrombin III and other inhibitors (in hepatic insufficiency and pancreatitis)

B. Increased clotting potential due to:
1. Thrombocytosis (following spleen removal)
2. Hyperfibrinogenemia (acute and chronic inflammatory processes, infections, metastatic tumors)

C. Hyperviscosity syndrome
1. Raised hematocrit (dehydration)
2. Paraproteinemia, dysproteinemia, cryoglobulinemia

the terminal circulation, a dominant role is played by flow changes and activation of the clotting system. In circumscribed arterial and venous thrombosis, changes in blood flow conditions and alterations in the vascular wall are of primary importance. Consequently, there are characteristic differences between arterial and venous thromboses.

Vessel Wall Lesions

Vessel-wall damage represents the initial thrombogenetic event in the arterial and venous sections of the vascular system. Significance attaches not only to large macroscopic or visible damage but also to microscopic and submicroscopic endothelial lesions. These are produced by hypoxia, endotoxins, antigen-antibody complexes, inflammatory changes in the vessel wall, mechanical stress due to trauma, and special flow conditions at branching sites and exits of vessels and in regions of turbulent blood flow. Leukocytes come into contact with the vascular endothelium at the periphery under certain flow conditions, and they can injure the endothelial cells and adversely affect the vascular integrity. Chemotactic substances are released by leukocyte disintegration and the secretion of constituent substances, and the chemotactic gradients between the perivascular space and the vascular lumen attract other cells, which in turn contribute to the vascular damage. Then the first of the platelets become attached to the damaged vascular endothelium and the exposed endothelial structures, with the occurrence of platelet clumping. Through involvement of the plasma clotting system, fibrin enters the developing thrombus following the development of traces of thrombin.

Circulation Conditions

The flow conditions have a decisive effect on thrombogenesis and on the characteristic structure of the thrombi in the individual vessel-regions. The rapid blood flow in the arteries and the flow conditions at the arterial exits lead to mainly platelet-rich thrombi. Fibrin structures are involved in the further development of so-called white thrombi.

Thrombi in the arterial section of the vascular system preferentially develop in the dilated atria in atrial fibrillation, in the left cardiac ventricle over the infarcted areas, at defective heart valves and valve protheses and over arteriosclerotic plaques in the aorta and the peripheral arteries.
As regards thrombogenesis the venous flow conditions with slower flow lead to increased involvement of the plasma clotting system, with the predominant development of a fibrin thrombus. The initial platelet thrombus preferentially occurs in the region of the vein valves, behind which a turbulent flow prevails with partial stagnation of the blood. Here, as mentioned, the accumulation of activated clotting factors may occur. Similar conditions can also arise in veins showing varicose enlargement. The white head of the thrombus follows the fibrin-rich and platelet-poor, erythrocyte-rich red tail of the thrombus in the direction of flow. Stasis alone is not sufficient to produce venous thrombosis. It has been shown by experiment that the blood does not clot in a vessel section which has been tied off. Clotting first occurs after trauma to the tissue in the corresponding vascular area or even in another part of the body. This indicates that other factors must be involved which alter the tendency of the blood to clot. The slowed blood flow in the veins of patients with cardiac insufficiency during bodily inactivity, postoperative immobilization, obesity, pregnancy, and puerperium, thus play an important part but not the only role in the development of thrombi. In the microcirculation hypoperfusion, stasis, and cell sludging, followed by hypoxia and acidosis, play decisive parts in activating the clotting system.

Changes in Vascular Content

Changes in vascular content are closely related to hypocirculation. Metabolites and components with a procoagulatory action (ADP, collagen, kinases, and enzymes) occur in hypoxically damaged vascular endothelium in the peripheral vascular region. The result is first that there is local hypercoagulability of the blood which can become systemic, and which can give rise to thromboses in remote regions if other factors are present. There can also be an increase in the hemostasis potential in infections and metastatic tumors (hyperfibrinogenemia, thrombocytosis), which increases the risk of the throm-

bosis. The loss of fibrinolysis activators in the endothelium, the decrease in antithrombin III, and reduced RES clearance capacity with accumulation of activated clotting products, tend to shift the equilibrium in hemostasis towards hypercoagulability. There are also changes in vascular content in polycythemia, increase in plasmaprotein, dysproteinemia, and para proteinemia, which affect the viscosity and the flow conditions and thus lead to a situation favoring thrombosis. The decisive factor however remains the interaction of several thrombogenic mechanisms.

Further Development of a Thrombosis

The fibrin in a thrombus adsorbs thrombin, plasminogen, and plasminogen activators with high affinity. The adsorbed thrombin is thus removed from the systemic circulation (fibrin is described as antithrombin I), which locally however promotes further fibrin production and thus the apposition of thrombotic material. In the subsequent course, the growth of the thrombus can be arrested by antithrombins. The thrombus can be lysed by plasmin, which has developed from adsorbed plasminogen with the aid of activators in the endothelium, and by proteolytic enzymes from blood cells. The thrombus can also become organized as connective tissue. Cells from the vessel wall and transformed monocytes from the blood are responsible for this process. Associated fibrinolytic processes provide for partial recanalization in the occluded vascular section. Smaller and larger fragments can also be released from a still unorganized thrombus and give rise to embolism.

Successful thrombolysis presupposes that plasmin will encounter a substrate which can be lysed in the thrombus. This is the case in venous thromboses, which mainly contain fibrin. The susceptibility to lysis is dependent on the age of the venous thrombosis. As the thrombus becomes increasingly organized as connective tissue, the chance for the vessel reopening is reduced. Thrombi in small vessels become organized earlier than those in larger ones. Stenoses and occlusions in the arteries arising from degenerative vascular diseases consist in part of arteriosclerotic plaques which cannot be lysed. The vascular changes become coated with thrombotic material, which leads to further narrowing and ultimately to occlusion of the lumen. Relatively

fresh arterial occlusions regularly contain thrombotic material. The proportion of platelets in a thrombus is higher in the arteries than in the venous part of the system. On the other hand, through the removal of the fibrin components, recanalization, and the dilatation of stenoses in the arteries become possible. Platelet thrombi can be fragmented by degradation of the fibrin components and thus removed. Here also, the susceptibility to lysis is dependent on the age of the thrombus and on the vascular lumen. It can be shown that the rate and completeness of the organization in an arterial thrombosis increases from a proximal to a distal localization and is mainly dependent on the vessel diameter. The organization of arterial thrombi takes place more slowly than that of venous thrombi. The former can be lysed for a considerably longer time after their development by comparison with the venous thrombi. Emboli arising from the heart and from thrombotic plaques of the aorta in the peripheral vascular region are more accessible to fibrinolysis than thrombi which have developed.

Usually, no fibrinolytic activity is detectable in the systemic blood. Plasmin which develops is instantly eliminated by inhibitors. The plasminogen coprecipitated with fibrin in the development of a thrombus and the endogenous plasminogen activators and any plasmin possibly produced are largely removed from the system by the inhibitors. After conversion from plasminogen, the plasmin can exert its action on the thrombus. This is the main cause of the spontaneous recanalization of thromboses, which quite commonly occurs to a varying extent in the venous system, whereas it is more rarely seen following the thrombotic occlusion of arteries. Plasminogen and activators can diffuse into a thrombus from the flowing blood and accumulate there. Investigations on thrombi obtained during operations indicate that directly after its development a thrombus is relatively rich in plasminogen, but in the subsequent 2–3 days it becomes low in plasminogen, and then accumulates plasminogen again up to day 7; after three months, hardly any fibrinolytic potential can be detected still in the thrombus. It is an open question how far these findings can be extrapolated to lysis *in vivo*. In principle, a thrombus can be lysed by plasmin from outside (exolysis) or in line with what has been said above from within (endolysis). Various views have arisen on the possibility of thrombus lysis following the infusion of activators (streptokinase, urokinase) (Fletcher and Alkjaersig, Ambrus and Markus, Chesterman). In principle, it can be assumed that streptokinase, the

streptokinase activator complex, urokinase, and also plasminogen and plasmin can diffuse into the thrombus and there become active. This has led to numerous suggested treatments aimed at the optimization of fibrinolysis.

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III. The Diagnosis of Coagulation Disorders

General Diagnosis

Hypocoagulability or hypercoagulability may occur as the result of any change in the hemostasis potential and any deviation in the hemostatic equilibrium from normal coagulability which exceeds a certain level. Depending on the extent of the disorder in the coagulation and fibrinolysis system and the availability of inhibitors of coagulation and fibrinolysis, the hypocoagulability or hypercoagulability may take a clinically latent course or become manifest in hemorrhagic symptoms and disorders of hemostasis, or else in the development of intravasal clotting processes and thromboembolic complications. The processes are affected by concomitant diseases and therapeutic measures which may be aimed specifically at the coagulation system or may affect the hemostatic system via side effects. Functional diagnosis of the hemostatic system has the following objectives:

1. Identification and differentiation of congenital and acquired hemorrhagic diatheses,
2. Identification of changes in the coagulation system favoring thrombosis, and
3. Therapeutic monitoring of:
   a) substitution treatment in hemorrhagic diatheses
   b) fibrinolysis and anticoagulant treatment in thromboembolic diseases.

Depending on the situation, the primary diagnosis involves the family and personal history in respect of previous bleeding, the identification of states resulting from previous bleeding or thromboses (joint

Table 1. Clinical symptoms of thrombocytic-vascular and plasmatic hemorrhagic diatheses

Type of bleeding	Thrombocytic-vascular bleeding condition	Coagulopathies
Frequency and severity of the hemorrhages		
Bleeding after superficial injury	Often profuse and prolonged	In general, not particularly pronounced
Contusions and hematomas	Small and superficial, frequently multiple	Often extensive and deep, usually localized
Skin and mucosal bleeding	Very frequent	Rare
Hemarthrosis	Very rare	Relatively rare, apart from congenital severe forms
Bleeding in deep tissue injuries, tooth extractions, etc.	In general immediately after the injury, frequently local treatment successful	Frequently late onset, local treatment unsuccessful
Most frequent manifestation		
	Purpura and ecchymoses, epistaxis, menorrhagia, gastrointestinal bleeding	Deep soft-tissue bleeding (evidently spontaneous or posttraumatic), skin and muscle bleeding, prolonged posttraumatic bleeding

changes in hemophiliacs, postthrombotic syndrome), and the analysis of the present circumstances which have led to the hemostatic disorder as well as the type of hemorrhage (Table 1). Coagulation disorders are characterized by extensive suffusion and bruises in the skin and mucous membranes and deep soft-tissue bleeding, which may occur spontaneously or after slight injury. If there are pronounced hemostatic defects, especially in hemophilia A and B, one frequently finds bleeding into the joints and meninges. Thrombocytic hemostatic disorders are characterized by petechial bleeding in the skin and mucous membranes. These occur particularly on the legs and arms, in the

nasopharyngeal space, and in the gums. Hemorrhages in the gastrointestinal tract are also found and frequently menorrhagia in women. Hemarthrosis is rare. Leaving aside major vascular malformations, which can lead to profuse local bleeding at the site of the vascular change, the vascular bleeding type corresponds to the thrombocytic type, with small circumscribed petechiae in the skin and mucous membranes. Acquired hemorrhagic diatheses frequently show uncharacteristic mixed symptoms.

The precise localization of the hemorrhagic diathesis or thrombophilia requires a special coagulation function analysis. The decisive factor is the selection of a suitable combination of tests, with which a small number of investigations such as the Quick value, PTT, and the thrombin time allow one to localize the defect in the hemostasis system in over 80% of cases (Fig. 1).

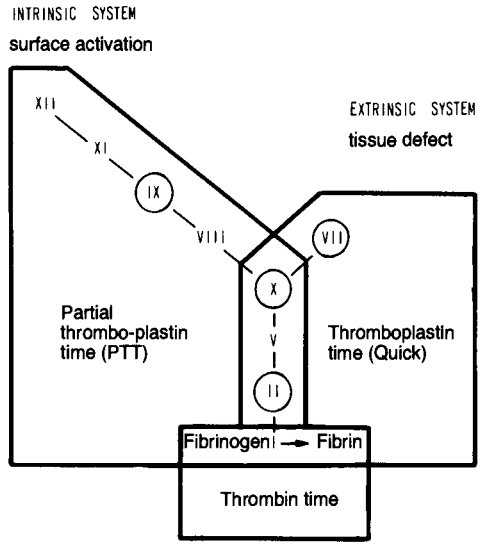

Fig. 1. Analysis of plasmatic clotting factors: in circles, factors dependent on vitamin K

Tests of Plasmatic Coagulation System Function

A prolonged *clotting time* is the characteristic feature of plasmatic coagulation disorders, namely coagulopathies in the narrower sense, with the exception of Factor VII deficiency. The precondition for a prolongation of the clotting time and of the fibrin-formation times in functional global and group tests is a decrease in the activity of the relevant clotting factor below a minimal value which lies at about 30% of normal. If the activity is higher than this, the tests do not usually serve to identify hemostasis disorders that involve one or more phases in the coagulation system. In such cases, only the determination of the individual factors can reveal the defect. Similarly, the coagulation disorder must have reached a certain level before a hemorrhagic diathesis becomes manifest. If one or more clotting factors have activities above a minimum limit, which varies from 10 to 30% for the individual factors, the hemostasis disorder remains clinically latent and only becomes apparent following injury, operation, parturition, and so on.

The tests of plasmatic system function have the purpose of differentiating the following disorders:

1. Disorders of prothrombin activation in the intrinsic and extrinsic system.
2. Disorders of fibrin formation consequent on coagulation- and fibrinolysis-specific changes in the coagulable substrate.
3. Changes in the inhibitor potential of the coagulation or the fibrinolysis.

Both qualitative and quantitative defects may be present. There are numerous immunochemical, physicochemical, chromatographic, and radio isotopic methods available for special diagnostic purposes and for elucidating scientific aspects, but these cannot be discussed in detail here.

The *whole blood clotting time* (5–10 min) covers hemostasis disorders due to defects in the sequence of the endogenous system, including the common terminal section (hemophilias, inhibitor hemophilias, hypofibrinogenemia, afibrinogenemia, and dysfibrinogenemia). To a certain extent, one can identify thrombocytic bleeding tendencies in defects concerned with the availability of procoagulation substances in the thrombocytes. Increased clotting times occur also with coumarin

derivatives (decrease in Factors II, IX, and X) and heparin. Factor VII deficiency is not indicated.

The *plasma recalcification time* (70–90 s) also concerns the intrinsic system. A Factor VIII concentration of ca. 10% is sufficient to produce an approximately normal recalcification time, so this test is not suitable for diagnosing hemophilia or monitoring treatment.

The *"clot observation"* test gives a crude and purely qualitative impression of the coagulation state. It does not require any accessories, but it should be performed only when there is no other possibility of clotting analysis. The thromboelastogram (TEG) and/or a few tests that do not require more time give more valuable results. The clot observation test is suitable if there is a known hemostasis disorder (e.g., consumptive coagulopathy) to estimate the relative importance of the contributions of clotting and fibrinolysis to the coagulation defect present. A local hemostasis disorder (e.g., local fibrinolysis) can be identified by comparing locally taken blood with systemic blood. To conduct the test, untreated blood is placed in a glass tube that is not siliconized, and one measures the time to the onset of clotting (about 6–10 min), retraction (after about 2 h), and the time to dissolution of the clot again (the clot is normally stable for hours).

Evaluation:

1. Slow clot formation and clot persistence: factor reduction in hemophilia and anticoagulant treatment, heparin, dysfibrinogenemia.
2. Normal clotting and dissolution of the clot within 2 h: increased fibrinolysis.
3. Delayed clotting and dissolution within 2 h: fibrinolysis with fibrin polymerization disorder due to fibrinogen-fibrin split products, and additionally under certain circumstances, hypofibrinogenemia due to fibrinogenolysis and/or lysis of factor V and VIII.
4. Absence of clotting: defibrination syndrome: lysis with high split product concentration, high heparin concentration.
5. Disordered retraction: mostly thrombopenia.

The *thromboelastogram (TEG)* permits a more differentiated and reproducible analysis of the entire endogenous clotting process, as well as the evaluation of fibrinolysis/fibrinogenolysis and trombocyte involvement. The r-time (reaction time, namely the time from blood sampling for untreated blood and for recalcification for citrated blood

or citrated plasma up to the reduction in light beam width to 1 mm) serves to measure the clotting time. r-time extension occurs in factor reduction in the endogenous system, heparin treatment, and fibrin polymerization disorders (dysfibrinogenemia, fibrin split products, paraproteins). r-time shortening occurs in hypercoagulability. The k-time (clot build-up time, time for 1–20 mm amplitude width) is increased in factor reduction, thrombopenia, thrombopathy, hypofibrinogenemia, heparin treatment, and fibrin polymerization disorders. It is shortened in hypercoagulability. The maximum amplitude m_a is reduced relative to the normal in thrombopenia, hypofibrinogenemia, dysfibrinogenemia, and in the presence of fibrinogen split products; m_a is increased in thrombocytosis, at high fibronogen concentrations, and when the hematocrit is low. A rapid decrease in the amplitude after ½–2 h indicates fibrinolysis activation, rarely a pronounced Factor XIII deficiency. The TEG shows no reaction in the absence of fibrinogen (defibrination syndrome, afibrinogenemia), in hyperfibrinolysis, and also high-dosage heparin treatment. A normal TEG does not rule out a slight hemostasis disorder. Thrombocyte functional disorders are not reliably picked up. Normal values for untreated blood: r-time 7–16 min, k-time 3–7 min, m_a 45–60 mm.

The *partial thromboplastin time* (PTT; normal value 30–45 s) evaluates the endogenous system, including the common terminal section with the exogenous system (Factors I, II, V, and X). The partial thromboplastin also corresponds to and replaces thrombocyte Factor 3 and is produced from thrombocytes, brain tissue, or erythrocytes. Activation by contact factors through kaolin or celite is necessary for the test. Usually, the so-called activated partial thromboplastin time (aPTT) is performed, where the commercial test kit contains phospholipid and contact-activating substances. The PTT is prolonged in hemophilia A and B and when there are reductions in the factors of the prothrombin complex (apart from Factor VII), provided that the factor activity is under 30% of normal. In addition, the PTT is prolonged in fibrinogen deficiency, fibrin polymerization disorders, and heparin treatment. PTT is suitable for checking hemophilia treatment and heparin therapy. It is shortened in hypercoagulability.

The *Quick test* (the prothrombin time; normal value 70–130%) reveals disorders in the exogenous system. The Quick test reagent contains tissue thromboplastin of varying origin (lungs, brain, and placenta)

and calcium. Otherwise it works with the factors in the plasma to be tested. The Quick value decreases in deficiency of one or several factors of the prothrombin complex (apart from Factor IX deficiency), reduction in the Factor V activity (deficiency or inhibitors), and hypofibrinogenemia or afibrinogenemia. It is affected by fibrin polymerization disorders (dysfibrinogenemia, split products, paraproteins) and by heparin. It is not possible to monitor fibrinolysis or heparin treatment on account of the poor correlation between the level of the amounts of split product of heparin and the prolongation of the prothrombin time.

The Thrombotest and Normotest test kits contain not only tissue thromboplastin and calcium but also Factor V and fibronogen. A deficiency of the latter factors is not indicated, in contrast to the Quick test. The Thrombotest is sensitive to what is called PIVKA (protein induced by vitamin K absence or antagonist). These in complete precursors are synthesized by the liver under coumarin treatment or in vitamin K deficiency (absorption disorder) and are not active in clotting, but they inhibit the clotting process because they have a structural resemblance to the complete factors of the prothrombin complex. For this reason the Thrombotest value is less than the Quick value under treatment with coumarin derivatives. With the Thrombotest there is a good correlation with the factor activity in the lower activity range so that anticoagulant therapy can be monitored closely. The Normotest shows a good correlation between factor activity and the measured times in the upper activity range. It is suitable for evaluating a moderate decrease in the factors of the prothrombin complex, e.g., in hepatic diseases. In contrast to the Thrombotest, it is insensitive to a Factor IX deficiency. The use of the Thrombotest and Normotest makes it possible to distinguish whether a reduction in the prothrombin complex factors is due to liver cell damage, vitamin K deficiency, or vitamin K antagonism due to coumarins. If the two tests are equally reduced, there is little or no PIVKA. Then probably one has liver cell damage. It should be mentioned that in hepatic cirrhosis also it is possible for the inactive precursors of the prothrombin complex (PIVKA) to be produced for various reasons. If the value in the Thrombotest is decidedly less than that in the Normotest, then a disorder of vitamin K metabolism is present. Heparin influences the Quick value and its modifications. Fibrin polymerization inhibitors play a part only at high concentrations.

In order to make the prothrombin time (PT) values during oral anticoagulation with coumarin derivatives comparable between different laboratories both nationally and internationally, the "international normalized ratio" (INR) was introduced in addition to and instead of the Quick value. After calibration to the WHO standard or the British Comparative Thromboplastin (BCT) the commercial thromboplastins are classified in accordance with an "International Sensitivity Index" (ISI). The INR is calculated using the equation: $INR = PR^{ISI}$. PR stands for PT ratio and means the quotient of the PT in seconds of the patient's plasma and of the laboratory's internal control plasma pool (PR = PT patient PT control). Depending on the indication used, the therapeuthic range lies between an INR of 2.0 to 4.5, as a rule between 2.5–4.0.

The *thrombin time* evaluates the last phase in clotting, namely the action of thrombin on fibrinogen and clot formation. The time is prolonged in fibrinogen deficiency (below 50–80 mg%), fibrin polymerization disorders (fibrin split products, dysfibrinogenemia, etc.) and with heparin.

The *reptilase time* is not affected by heparin, but is otherwise subject to same conditions as the thrombin time. The combination of the two tests during heparin treatment allows this to be monitored as well as providing information about an accompanying fibrinolysis.

These tests use the occurrence of a fibrin polymerizate or clot for the end point determination, which is formed from fibrinogen present in the patient's plasma or added to the sample. It should be noted that the occurrence of the fibrin clot is evaluated in different ways in accordance with a particular laborator's methods (visible clot when determined by hand; measurement of the firmness of the fibrin clot, the conductivity, or the light transmission). This leads to values that are not directly comparable.

With a combination of the PTT, the Quick test, and the thrombin time, which are simple and can be quickly carried out, one can cope with the main emergency situations of hemostasis type (Fig. 1). Individual factor determination is required for the detailed localization of the hemostatic defect and the determination of its magnitude. There are commercial test kits that use deficient plasmas for these factors.

Numerous methods are available for *fibrinogen determination:*

1. Immunological techniques: radial immunodiffusion, Laurell electrophoresis.

2. Measurement of the coagulable protein: the clot induced by thrombin in a defined amount of plasma is isolated. The protein content is measured by direct photometry at 280 nm after solubilisation of the clot, e.g. in 6 M urea – 0.2 M NaOH solution, or else the clot is first dissolved in caustic soda solution and after reaction with biuret or phenol reagent evaluated in the visible range of the spectrum.
3. Turbidity measurement: the plasma diluted 1:10 is mixed in a cell with small amounts of thromboplastin or thrombin and the turbidity is recorded by photometry. This is related to the fibrinogen concentration present.
4. Nephelometric methods after the addition of a specific antibody and measurement of the nephelometric effect due to the antigen-antibody complexes.
5. Clauss's method: rapid clotting of a plasma diluted 1:10 due to high thrombin concentrations. The clotting time is related to the fibrinogen concentration.
6. Schulz's heat fibrin: crude quantitative measurement of the protein precipitated in 10 min at 56°.
7. Sodium sulfite precipitation of the fibrinogen and photometric estimation after redissolving of the precipitate.

Methods 1, 2, and 7 are time-consuming and require several working steps. Method 5 is affected by split products and heparin. Method 6 is dependent on the electrolyte and protein contents and also on the split product concentrations in the plasma and gives poor reproducibility. Clauss's method and the turbidity measurement after the addition of thrombin are relatively rapid to carry out and give adequately accurate values. For special investigations (e.g. dysfibrinogenemia) one may need to combine the various functional and immunological methods.
A clinically relevant Factor XIII deficiency (namely less than 2% of the norm; secondary bleeding 3–5 days following operations; wound healing disorders) can be identified qualitatively from the solubility of a clot in 5M urea, 0.1M monoiodoacetic acid, or 2% acetic acid. Test kits are available for precise quantification.
The *ethanol gelation test* (gel-type fibrin precipitation from plasma with ethanol: 0.5 ml plasma + 0.15 ml of 50% ethanol, left standing for 10–15 min at room temperature) and the *protamine sulfate test* (amorphous or fibrous precipitate produced by fibrin precipitation with protamine: 0.5 ml of plasma + 0.05 ml of 1% protamine sulfate

left to stand for 15 min) are considered to be indicators of the fibrin dissolved in the plasma in states with increased intravascular turnover of clotting factors (chronic and acute consumption reactions, possibly also hypercoagulability). These are so-called paracoagulation phenomena. The fibrin dissolved in the plasma as a complex with fibrinogen and/or fibrinogen split products is precipitated as a result of charge change and water loss. The ethanol test is sometimes known to give false positive results at high fibrinogen concentrations (over 400–500 mg%) and in paraproteinemia, as well as false negative results at very low fibrinogen concentrations (less than 60 mg%) and in the presence of large amounts of split products.

Test Methods for the Fibrinolytic System

To estimate fibrinolytic activity in the plasma and to monitor fibrinolytic or antifibrinolytic treatment, it is sufficient to measure prolongation of the thrombin and/or reptilase times. Fibrinogen/fibrin split products in the plasma interfere with fibrin polymerization and prolong the onset of clotting in the test system.
It is possible to quantify the fibrinogen/fibrin split products by:

1. tanned red cell hemagglutination inhibition immunoassay (TRCHII test, Wellcome)
2. latex agglutination test (Wellcome)
3. staphylococcal clumping test (Behringwerke, Boehringer)
4. Laurell electrophoresis
5. immune precipitation.

To avoid interference with fibrinogen, the test must be carried out in the serum. There are possibilities of error in that some of the split products, particularly the macromolecular ones, are incorporated into the clot during production of the serum, and minimal amounts of fibrinogen or fibrin persist as complexes with split products dissolved in the serum. Preference should be given to the latex agglutination test and the staphylococcal clumping test in the routine laboratory because they are simple to carry out. The two tests detect with decreasing sensitivity fibrinogen, and the split products X, Y, and D. E is detected most weakly or not at all. Other methods for evaluating the fibrinolytic potential are the estimation of the euglobulin lysis time and of plas-

minogen, the latter by immunological methods or by means of chromogenic substrates.

Platelet Function Tests

Rumpel-Leede capillary resistance: the test is positive in generalized diseases of the capillary system (toxic; antigen-antibody reaction, C-avitaminosis), in thrombocytopenias under 30000–50000 per mm^3, and sometimes also in thrombopathies. Positive results can also occur in hyperfibrinolysis and as an expression of a combined vascular and platelet function disorder, as well as in uremia, paraproteinemia, and dysproteinemia.

The *bleeding time* can be measured in various modifications by Duke, Ivy and Mielke (normal value roughly between 2 and 6 min.). It is prolonged in thrombopenias below 30–50000 per mm^3 of various etiologies (Werlhof's disease, drugs, and after multiple transfusion of old blood lacking functional platelets), and also in thrombocythemia, congenital thrombopathies (von Willebrand-Jürgen's syndrome; Glanzmann-Naegeli thrombasthenia), and in acquired platelet defects (e.g. aggregation inhibitors, antiinflammatory drugs, analgesics, penicillins, cephalosporins, dysproteinemia and paraproteinemia, and uremia). As a rule, the bleeding time in coagulopathies is not prolonged except in distinct hypofibrinogenemia, afibrinogenemia, hyperfibrinolysis, and high-dosage heparin treatment. It is occasionally prolonged in angiolopathies. Measurement of the bleeding time is indicated for testing the platelet hemostatic potential, and also as a supplementary measure in checking for hemostasis before puncture etc., as well as in monitoring treatment of thrombopenia and thrombopathies. No utilizable results are obtained from the bleeding time in hypocirculation and shock.

Several methods have been reported for measuring *platelet aggregation.* This can be induced with adenosine diphosphate (ADP), collagen, ristocetin, adrenaline, etc. Through use of various proaggregatory stimulators, conclusions can be drawn to some extent about the cause of the impaired thrombocyte function.

Platelet retention and *adhesion* are measured on glass slides, glass wool, small columns containing glass beads, etc. These methods are important for the differentiation of rare, mostly congenital defects of

platelet function. In this connection, mention should also be made of the determination of the availability of platelet Factor 3.
Recently it has become possible to measure the thrombocyte constituents *β-thromboglobulin* and *platelet Factor 4* by immunological means on plasma. The concentrations of these provide certain information about thrombocyte activation with release reactions in vivo.
A platelet count of less than 30000 per mm^3 (normal range between 150000 and 300000 per mm^3) is mostly associated with petechial and mucosal hemorrhages. If there is additional qualitative damage to the thrombocytes, there may sometimes be hemorrhagic diathesis even at 100000 per mm^3.
The in vitro thrombocyte function tests usually do not provide any quantitative indication of the platelet behavior in vivo. Only subject to considerable reservations do they give an indication of the extent of the hemorrhagic diathesis. Their importance lies in the differentiation of congenital and acquired functional disorders.

Extended Coagulation Analysis

Besides the global and group tests the determination of individual factors of the clotting, fibrinolysis and their inhibitors is possible. Factors of the coagulation system can be quantified with the use of appropriate deficient plasma.
Immunological procedures (radial immunodiffusion, nephelometry, radioimmunoassay, Laurell electrophoresis, enzyme-linked immunosorbent assay, ELISA) and chromogenic substrates are increasingly being used in the analysis of the hemostasis system.
Chromogenic substrates are tri- or tetrapeptides the amino end of which is substituted and thus blocked in such a way that enzymatic cleavage is possible only at the para-nitroaniline amide-like bound carboxyl end. Proteases can split this amide bond. The color intensity of the released nitroaniline can be measured by photometry. The amino acid sequence of the chromogenic peptides exhibits a composition which corresponds structurally to the area of the substrate molecule, with the cleavage taking place through the special proteases. If arranged as two-stage procedures the tests can also be used for the enzymatic determination of nonactive coagulation proteases.

With the use of the procedures mentioned, inter alia the following parameters of the hemostasis system can be measured:
Immunologically: concentration of individual clotting factors; concentration of antithrombin III, protein C, plasminogen, alpha$_2$-antiplasmin, C_1 inactivator, alpha$_2$-macroglobulin, histidine-rich glycoprotein, fibrinopeptide A, fibrinogen peptides B_β 1–42 (plasmin-induced) and β 15–42 (plasmin- and thrombin-induced), thrombin-antithrombin III-complex, plasmin-α_2 antiplasmin-complex, elastase-α_1 antitrypsin-complex, β-thromboglobulin, platelet factor 4.
Chromogenic substrates: Quick, PTT, activity of individual clotting factors; activities of antithrombin III, protein C, plasminogen, alpha$_2$-antiplasmin, C_1-inactivator, tissue plasminogen activator (tpA), anti-tpA, prekallikrein, heparin, urokinase.

Interpretation of Clotting Findings

Table 2 gives a program for analyzing clotting. The parameters in the box also indicate assessment of platelet hemostatic function and represent a minimal program. The thromboplastin time, Quick value, and thrombin time (Fig. 1) give a suitably precise indication of the hemostatic potential and the possible tendency to bleeding. The prog-

Table 2. Program for evaluating the most important hemostasis disorders (minimal program in box) (Matthias and Lasch 1979)

1. Quick
2. Partial thromboplastin time
3. Thrombin time
4. Thrombocyte count
5. Bleeding time
6. Factor VIII
7. Fibrinogen

8. Reptilase time
9. Ethanol test
10. Thrombelastogram
11. Platelet aggregation

ram can be appropriately extended to localize the diagnosis and can be supplemented by additional individual-factor determinations. As the Quick value, PTT, and thrombin time determinations are dependent on the subject's own fibrin, it is recommended that a fibrinogen determination should be made in order to exclude a fibrinogen deficiency. The reptilase time serves to evaluate associated fibrinolysis during current heparin treatment. Factor VIII, in addition to the changes in the above parameters, provides an important indicator for discriminating between liver function disorder and consumptive coagulopathy. Coagulation activation in the sense of hypercoagulibility and a consumptive reaction can be demonstrated by the ethanol gelation test. Hypercoagulability is not detectable in the usual methods by clotting analysis.

Table 3 lists the altered clotting parameters in these tests in relation to the deviations in the hemostatic equilibrium from normal coagulability given in Table 5. By *increased coagulation potential*, we mean increased available amounts of potentially coagulation active material, especially fibrinogen and platelets. This term does not imply information about whether activation of clotting may have already taken place. An increased coagulation potential tends to favor thrombosis on account of changes in the flow behavior of the blood and through the increased presence of a substrate capable of clotting. Fibrinogen can increase as an acute-phase protein in infections, cardiac infarction, etc. Thrombocytosis occurs in certain hematological diseases and after splenectomy. *Hypercoagulability* is a state of increased liability to coagulation, and it implies an intravascular state with facilitated activation of the coagulation system and accelerated clot production. Here there may also be a latent activated coagulation system with limited thrombin effect, which is identifiable from the soluble fibrin in the plasma. This constellation is observed inter alia following cardiac infarction, in the initial phase of shock, with tumors etc. In circulatory shock, sepsis, hepatic cirrhosis, and many other diseases, there can be excessive systemic progressive activation of coagulation leading to an increase in turnover of the coagulation factors giving rise to the exhaustion and collapse of the hemostasis system, seen on coagulation analysis from the decreases in and prolonged times of the test parameters mentioned. A consequence of *disseminated intravascular coagulation* is an increased tendency to bleeding *(consumption coagulopathy)* with or without disseminated

Table 3. Changes in coagulation analysis parameters in common hemostasis disorders (Matthias and Lasch 1979)

A. *Increased coagulation potential*
1. Fibrinogen raised
2. Platelet count raised
3. Maximal amplitude in TEG widened (consequence of 1 and 2)

B. *Hypercoagulability*
1. Shortened: clotting time, PTT, thrombin time, r-time in TEG
2. Raised Factor V and Factor VIII activities
3. Optional: positive ethanol test

C. *Consumption reaction*
1. Reduced: platelet count, Factors I, II, V, VIII and XIII
2. As consequence of 1: Quick reduced, PTT prolonged, thrombin time prolonged (rare)
3. Positive ethanol test
4. TEG altered

D. *Fibrinolysis*
1. Prolonged: thrombin time, reptilase time, PTT
2. Reduced: fibrinogen
3. Possibly Quick moderately reduced

E. *Heparin*
1. Prolonged: thrombin time, PTT
2. Possibly Quick moderately reduced
3. TEG changed

F. *Coumarins*
1. Reduced: the Quick test and its modifications
2. Prolonged: PTT at high coumarin doses
3. TEG altered

G. *Hemophilia*
1. Prolonged: PTT
2. TEG altered

H. *Platelet function disorder*
1. Reduced: aggregation (collagen, ADP, adrenaline, ristocetin)
2. Prolonged: bleeding time
3. TEG altered

intravascular fibrin deposition *(microthrombosis)*. The increased turnover of coagulation factors occurs acutely within an hour or so, or may take a more chronic compensated course. In the latter case, one detects only moderate pathological changes in the clotting parameters

with a more latent bleeding tendency. Serial analyses are required to evaluate the course. A progressive decrease in the platelet count and a positive ethanol test provide valuable evidence. The other hemostasis disorders given in Table 3, apart from hemophilia, are mainly iatrogenic and can be identified by means of the above basic coagulation analysis program from the changes in the specified parameters, particularly in the group tests.
Table 4 gives the converse of Table 3 as a survey of the causes leading to changes in the individual clotting parameters. The concentrations

Table 4. Causes of changes in some clotting test parameters (Matthias and Lasch 1979)

A. *Quick (reduction)*
1. Reduction in prothrombin complex:
   a) synthesis disorder, b) consumption reaction
2. Heparin > 1 unit/ml of plasma
3. Fibrinolysis: > 50 µg of split products per ml of plasma (normal up to ca. 3 µg/ml)
4. Hypofibrinogenemia, dysfibrinogenemia (polymerization disorder)
5. Paraproteinemia (polymerization disorder), plasma expanders

B. *PTT (prolongation)*
1. Hemophilia, von Willebrand-Jürgen's syndrome (factor activities less than 10–20% of normal)
2. Reduction in prothrombin complex
   a) synthesis disorder, b) consumption reaction
3. Heparin > 0.2–0.5 unit/ml in plasma
4. Fibrinolysis: > 50 µg of split products per ml of plasma
5. Hypofibrinogenemia, dysfibrinogenemia (polymerization disorder)
6. Paraproteinemia (polymerization disorder), plasma expanders

C. *Thrombin time (prolongation)*
1. Heparin: > 0.2–0.5 unit/ml of plasma
2. Fibrinolysis: > 50 µg of split products/ml plasma
3. Hypofibrinogenemia (< 50 mg %), dysfibrinogenemia
4. Paraproteinemia, plasma expanders

D. *Reptilase time (Prolongation)*
1. Fibrinolysis: > 10–30 µg of split products per ml of plasma
2. Not influenced by heparin, otherwise as for thrombin time

E. *Ethanol test (positive)*
1. Hypercoagulability
2. Consumption reaction.

given can be used as guideline values. In individual cases, they vary somewhat with the methods used.

Table 5 gives the most common situations showing altered coagulation analysis parameters. The causes listed under points 1 to 4 are those mainly observed in practice. It should be noted that heparin administered subcutaneously is increasingly being used on outpatients as well as thrombosis prophylaxis with coumarin derivatives. Unexpected hemorrhagic diatheses are frequently to be explained by the fact that in known hemostasis defects (hepatic cirrhosis or coumarin treatment) the treating doctor did not know that certain other drugs were being taken, which have an undesired side effect on the hemostasis system.

Clotting analysis is indicated as follows:

1. if there is evidence from the history and clinically of increasing hemostasis disorder,
2. preoperatively,
3. before invasive diagnostic procedures (liver biopsy or angiography), and
4. postoperatively if there is circulatory insufficiency or a shock situation.

In minor operations without danger of uncontrollable bleeding, and if there is no evidence of a hemostasis disorder, one can employ a reduced program under certain circumstances (Quick value and bleeding time), or it is even possible to dispense with clotting analysis

Table 5. Commonest situations with altered clotting parameters (Matthias and Lasch 1979)

1. Anticoagulants (coumarin derivatives, heparin)
2. Platelet aggregation inhibitors (acetylsalicylic acid, sulfinpyrazone)
3. Numerous drugs (analgetics, antirheumatic drugs, penicillins)
4. Hepatic parenchymal damage, hepatic cirrhosis: (synthesis disorders: hepatic, vitamin K absorption disorder; turnover disorders: hypercoagulability, consumption reaction, fibrinolysis)
5. Hemophilia, von Willebrand-Jürgen's syndrome
6. Parenteral nutrition, malabsorption syndrome (vitamin K deficiency)
7. Circulatory shock (hypercoagulability, consumption reaction, fibrinolysis)
8. Multiple trauma (hypercoagulability, consumption reaction)
9. Multiple transfusion (decreases in factors in platelets, "washout effect", consumption reaction)
10. Cardiac surgery, extracorporeal circulation (turnover increase, fibrinolysis, heparin, and protamine chloride overdose).

Table 6. Causes of pathological coagulation analysis parameters (Matthias and Lasch 1979)

1. Defect in clotting system
2. Blood: citrate ratio of 9:1 altered (faulty blood sampling, and marked deviation of hematocrit from normal)
3. Inadequate mixing of blood after sampling (partial clotting of blood sample)
4. Long storage of blood sample before analysis (over 2h)
5. Temperature variation of water bath during blood sample storage
6. Heparin instead of citrate as anticoagulant
7. Infusion of heparin by venous catheter before blood sampling
8. Measurement error in laboratory

altogether. The frequency of clotting determinations is controlled by the clinical picture and the course of any detected clotting disorder. Table 6 gives a survey of the causes of unexpected findings in clotting analysis.

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A. Hemorrhagic Diatheses

Introduction

Three types of hemorrhagic diatheses can be distinguished:
1. Coagulopathies (plasmatic clotting disorders)
2. Thrombocytic clotting defects (thrombocytopenia, thrombocytopathy)
3. Tendencies towards vascular bleeding

Vascular hemorrhagic diatheses cannot be determined by analysis of coagulation. In plasmatic and thrombocytic coagulation disorders there are quantitative and/or functional defects of one or more components of the coagulation system. The extent and combination of the defects in the coagulation system determine the degree of hypocoagulability of the blood, and also the clinical manifestation of the hemorrhagic diathesis. An increased tendency to bleed generally appears only when the individual clotting components have reached their lowest hemostatic activity. Similarly, in the case of moderate disturbances in the hemostatic system the global and group-specific functional test results are still in the area of normality. Functional damage to a clotting component is apparent only in the analysis of individual factors. Defects of formation and turnover are distinguished.

General Clinical and Diagnostic Approach

In the case of an evident hemorrhagic diathesis, the first identification of the underlying defect in the hemostatic system is arrived at through

the type of bleeding (Table 1/III). It is important to establish the moment in time and the type of the first manifestation, the frequency of recurrences, and, in addition, whether it is a so-called spontaneous hemorrhage after small lesions that have gone unnoticed or an increased tendency to bleed during or after surgical intervention, or whether permanent damage occurs after bleeding (ankylosis, hemarthrosis, nerve damage). If congenital hemostatic disturbance is suspected, an exact family history is necessary. Congenital hemorrhagic diatheses show as a rule repeated characteristic bleeding symptoms. Acquired tendency to bleed often shows only uncharacteristic changing hemorrhagic phenomena. In any case an exact localization of the clotting defect and its extent from a diagnostic, therapeutic and prognostic point of view is necessary. For a definite diagnosis the following parameters are necessary (Table 2/III):

1. Determination of the capillary resistance (Rumpel-Leede test)
2. Time of bleeding
3. Thrombocyte count
4. Thromboplastin time
5. Partial thromboplastin time
6. Thrombin time
7. Ethanol gelation test

With this combination of tests, about 80% of clotting defects can be pinpointed, and sufficient indications gained for emergency treatment and its supervision. There is a loose connection between the degree of deviation from the norm in the analytical tests mentioned and the extent of the hemorrhagic diathesis which appears clinically. An exact determination of the defect in hemostasis demands determination of individual factors, the use of immunological tests of the plasmatic and thrombocytic clotting system, and special procedures for investigating the function of the thrombocytes and the constituents of the thrombocytes as well as of the bone marrow.

IV. Coagulopathies

Definition

The pathogenetic principle of plasmatic clotting disorders is the reduced or missing activity of one or more plasmatic factors during the coagulation process in vivo. Reduced activity may be caused

1. by a quantitative reduction in the factor or factors concerned, either through reduced synthesis or as a result of increased turnover,
2. by a qualitative defect in the protein structure of the clotting factor, which prevents normal activity or function,
3. by the presence of an inhibitor in the plasma which blocks the development of the activity.

The defect may be localized in one or more different phases of the coagulation process by a disturbance

1. in the formation of the prothrombin activator of the extrinsic or intrinsic system,
2. in the formation of thrombin,
3. in the formation of fibrin.

Tables 1 and 2 give a summary of plasmatic coagulation disorders.

Table 1. Clotting factors and their relationship with hemorrhagic diatheses (Deutsch, 1973, VII)

Clotting factor	Name	Clotting disorder	
		Congential	Acquired
I	Fibrinogen	Afibrinogenemia hypofibrinogenemia dysfibrinogenemia	Consumption coagulopathy fibrinogenolysis
II	Prothrombin	hypoprothrombinemia Dysprothrombinemia	Vitamin K deficiency of the newborn Coumarin derivatives Parenchymatous liver damage Consumption coagulopathy
III	Tissue Thrombokinase		
IV	Calcium		
V	Proaccelerin	hypoproaccelerinemia (parahemophilia)	Consumption coagulopathy fibrinolysis Parenchymatous liver damage
VII	Proconvertin	Hypoproconvertinemia Dysproconvertinemia	Vitamin K deficiency of the newborn Coumarin derivatives Parenchymatous liver damage
VIII	Antihemophilic Globulin A	Hemophilia A von Willebrand-Jürgens syndrome	Consumption coagulopathy Fibrinolysis Macroglobulinemia Inhibitor
IX	Antihemophilic Globulin B	Hemophilia B von Willebrand-Jürgens syndrome	Vitamin K deficiency of the newborn Coumarin derivatives Parenchymatous liver damage Inhibitor
X	Stuart-Prower factor	Stuart-Prower factor deficiency	Vitamin K deficiency of the newborn Coumarin derivatives Parenchymatous liver damage

Table 1. (Continued)

Clotting factor	Name	Clotting disorder	
	Congential	Acquired	
XI	Plasma thrombo-plastin antecedent	PTA deficiency	Parenchymatous liver damage
XII	Hageman factor	Hageman factor deficiency	Parenchymatous liver damage
XIII	Fibrin stabilizing factor (FSF)	FSF deficiency	Consumption coagulopathy Parenchymatous liver damage
	von Willebrand factor (factor $VIII_{vWF}$)	von Willebrand-Jürgens syndrome	

Table 2. Classification of coagulopathies

A. Disorders of formation
  I Congenital coagulopathies
    a) Hereditary X-chromosomal recessive
      Hemophilia A
      Hemophilia B
    b) Hereditary autosomal recessive
      Deficiency of factors II, V, VII, X, XI, XII, XIII, I
    c) Without definite hereditary factor
      Combined factor deficiency
    d) Hereditary autosomal dominant
      Dysfibrinogenemia
      von Willebrand-Jürgens syndrome
  II Acquired coagulopathies
    Hypothrombinemia
      Prothrombin complex deficiency of the newborn
      Disturbances in vitamin K absorption and utilization in adults
      Reduction in prothrombin complex through antibiotics
      Anticoagulation therapy with coumarin derivatives
B. Disorders of metabolism
  I Consumption coagulopathy and secondary fibrinolysis
  II Primary hyperfibrinogenolysis
  III Hemorrhagic diathesis in monoclonal gammopathy
  IV Immune coagulopathies

Abnormalities of Synthesis

Congenital Abnormalities of Synthesis

X-chromosomal Recessive Group – Hemophilia A and B

Definition and Pathogenesis
Hemophilia A and B are congenital hemorrhagic diatheses with sex-linked recessive inheritance. It follows that

1. the hemophilic tendency to bleed appears only in the male sex
2. the marriage of a hemophiliac with a healthy woman produces healthy male offspring; all female offspring are carriers (heterozygotic, as a rule without clinical manifestation of a tendency to bleed despite a 50% activity of factors VIII or IX)
3. from the marriage of a carrier with a healthy man, the male offspring have an equal chance of being healthy or hemophiliac, and similarly the female offspring have an equal chance of being healthy or carriers

In rare cases a hemophilic tendency to bleed can also occur in women:

1. in a carrier with factor VIII activity below 25%,
2. in the daughter of a hemophiliac and a carrier,
3. in true hemophilia, which may occur sporadically,
4. in hemophilia of a phenotypically female individual with male sex chromosomes.

In 30% of cases it is hemophilia A, and in about 9% it is hemophilia B which occurs sporadically.
The following conditions must hold for a woman to be identified as a carrier:

1. she is the daughter of a hemophiliac,
2. she is the mother of more than one hemophiliac son or more than one daughter diagnosed as a carrier,
3. she is the mother of a hemophiliac son, and in addition has a familiy relationship with another hemophiliac, which comes within the hereditary pattern of hemophilia.

Carriers have a factor VIII or IX activity of about 50%. As the activity of the factors can fluctuate physiologically, and the determination of

the clotting factor by analysis has a certain range of error, additional immunological procedures with determination of the relationship of factor VIII activity to the concentration must be carried out. Identification of a carrier is possible in about 89% of cases.
The factor VIII molecule consists of two components. A smaller part with a molecular weight between 100000 and 200000 carries the coagulant activity. It can be neutralized by homologous antibodies. The larger part of the molecule, with a molecular weight of about 1000000, possesses no coagulant activity, but is necessary for the function of the platelets in the interaction of the thrombocytes with the vessel wall. In the von Willebrand-Jürgens syndrome it is reduced. This so-called factor VIII antigen is identical with the functional characteristics of the von Willebrand factor and the ristocetin aggregating factor. Heterologous antisera not only inactivate factor VIII activity, but at the same time precipitate factor VIII antigen. In 85 to 95% of patients with hemophilia A, the functional factor VIII activity and the protein part which reacts with homologous antisera are reduced. In the remaining 5 to 15% of patients with hemophilia A there is a so-called cross-reacting material (CRM) which neutralizes homologous antibodies but has no coagulating activity. It is assumed that in this case the smaller component of the factor VIII molecule is deformed, and has antigenic properties, but no functional effect. The larger, first-mentioned group of patients is referred to as hemophilia A− or CRM−, and the last-mentioned as hemophilia A+ or CRM+. Unlike the von Willebrand-Jürgens syndrome, in hemophilia A the factor VIII antigen, i. e. the higher molecular-weight part, is present in normal concentration.

Clinical Findings and Diagnosis

In the Federal Republic of Germany there is one hemophiliac to every 10000 people, that is to say there are 6000 patients known to have this hemorrhagic diathesis. In 85% it is hemophilia A and in 15% hemophilia B. The figures are approximate, as mild forms of hemophilia are not identified in every case. Rather schematically, corresponding with the reduction in activity, three degrees of severity are distinguished:
1. the severe form with a factor activity of below 1%

2. the moderately severe form with a factor activity between 1% and 5%
3. the mild form with a factor activity between 5% and 25%.

50% of the cases of hemophilia diagnosed are of the severe form. About 50% of the severe forms of hemophilia are diagnosed at the end of the first year of life. Moderate and mild forms are recognized later, often as a result of injuries and operations. Subhemophilia with factor activity between 25 and 50% plays scarcely any part clinically. Prolonged bleeding from the stump of the umbilical cord and after circumcision give the first indication in small babies. Hemophilic bleeding shows itself clearly in childhood. After slight bruises, and also without any noticeable signs of injury, there is prolonged bleeding from the skin and soft parts. Whereas in deep wounds the internal blood loss may lead to a shock to the circulation, superficial injuries often do not cause severe secondary bleeding. In adults there is often bleeding from the joints, especially the large joints, and later secondary damage. Further bleeding points are the ilio psoas muscle, the retroperitoneal cavity, the intestinal wall and the brain. Intracerebral bleeding is observed in 10% of cases. Bleeding in the floor of the mouth and the area of the larynx and the pharynx are especially dangerous. The hemophilic pseudotumor which is observed, particularly on the os ileum and the femur, after internal bleeding with subsequent pressure necrosis, may be confused with bone tumors. Hematuria is common.

After the hemophilia has manifested itself there is a variable prolongation of the partial thromboplastin time, which does not become pathological until the factor VIII activity has fallen below the minimum concentration of 15 to 20%. Quick value, thrombin time and bleeding time are normal. After the addition of normal serum to the patient's plasma a prolonged partial thromboplastin time in hemophilia A cannot be corrected, as there is no more factor VIII activity in the serum. But correction by normal serum succeeds in the case of hemophilia B as the factors of the prothrombin complex are present in active form. An exact differentiation and determination of the severity of hemophilia is achieved by individual analysis of factors VIII or IX. In severe hemophilia A, inhibitors in the form of neutralizing antibodies occur in 5 to 20% of the patients. The inhibiting substance is directed against the coagulating activity. The neutralization of

factor VIII activity is time-dependent and reaches a balance after one to two hours. In hemophilia B inhibitors are observed only in 1 to 3% of patients, and in the subgroup with severe hemophilia B in about 12%. Inhibitors appear as a rule during the first 100 transfusions. Substitution therapy with factor concentrates increasingly loses its effect. The inhibitor is without influence on the clinical symptoms of the hemorrhagic diathesis with regard to type of bleeding and frequency of recurrence. Without substitution, in about ¾ of the patients there is a spontaneous drop in the inhibitor of 50% per month. After about six months to two years it is no longer demonstrable. After further substitution we can expect a rise in the inhibitor after 5 to 6 days, which reaches its maximum after 1 to 3 weeks. About 30% of the patients are known as "low responders"; in them the inhibitor, even with continuous substitution, does not exceed 5 to 10 Bethesda or New Oxford units. The remaining patients are called "high responders"; in them the inhibitor titer may exceed several hundred up to over a thousand Bethesda or New Oxford units. The diagnosis of hemophilia with inhibiting substance is made through the ineffectiveness of substitution therapy, the plasma change test and the quantitative determination of the inhibiting activity.

Treatment

For emergency treatment fresh plasma, fresh-frozen plasma and cryoprecipitates are suitable for hemophilia A and prothrombin complex preparations for hemophilia B. Purified factor concentrates are to be preferred in any case. In hemophilia A the factor VIII activity in the plasma is raised by 1 to 2% by one unit of factor VIII per kg of body weight. In hemophilia B one unit of factor IX per kg of body weight raises the factor IX level by a maximum of 1% only. This is due to the low in vivo recovery of factor IX, from 20 to 50%, in comparison with that of factor VIII, from 50 to 60%. In accordance with the biological half-life, ½ to ¾ of the initial dose in hemophilia A is to be injected about every 8 hours, in hemophilia B about every 12 to 24 hours. In the case of small hemorrhages without complications, sufficient activity of about 20% is obtained with an initial dose of 20 to 25 units of factor VIII or factor IX per kg of body weight. The maintenance dose is 10 to 12 units of factor VIII or factor IX per kg of body weight at the

intervals in time given above. Control by coagulation analysis follows with determination of the activity of factor VIII or IX and/or the measurement of the partial thromboplastin time, which should be below 60s (normal value 45s).

Different forms of treatment are practised, depending on the degree of organization of the hemophilia center, the distance of the patient's home from the doctor's practice or the hospital, the patient's readiness to cooperate and the severity of the hemophilia and the frequency of bleeding. When treatment is given by the doctor exclusively, it must be accepted that there are as a rule greater blood losses, which in some circumstances are a risk to patients, prolong treatment, and if there is bleeding from the joints, have an unfavorable effect on hemophilic arthropathy. In controlled self-treatment (home treatment), at the first sign of bleeding the patient himself or his relatives can carry out a factor substitution which can stop the bleeding in the initial phase. It is presupposed that the patient can recognize the start of bleeding with sufficient certainty, and can judge the necessity of treatment. A subsequent check or a continuation of treatment should be carried out by the doctor. In continuous treatment, as a rule factor concentrates are injected by the patient himself at regular intervals even when there is no bleeding. The amounts to substitute in hemophilia A lie between 36 and 45 units of factor VIII per kg of body weight per week, divided into 2 to 3 single injections. In hemophilia B 9 to 18 units of factor IX per kg of body weight per week are necessary, given in 1 to 2 injections. Occasionally injections are only necessary at intervals of 2 weeks.

Table 3 gives, for various types of bleeding, the average necessary plasma level of the factors, and the average duration of substitution. In self-treatment for bleeding from the joints, often only one injection is necessary until the bleeding stops. For tooth extraction an additional dose of antifibrinolytics (epsilon aminocaproic acid, 6–12 gr per day, tranexamic acid 1–2 gr per day) may be useful (Table 4). These drugs are given on the assumption that local secondary fibrinolysis is suppressed. Fibrin adhesives are an additional possibility. Bleeding into the iliopsoas muscle is particularly dangerous, because it cannot be watched and there is the possibility of nerve damage; it should always be treated in hospital. In bleeding from the floor of the mouth there is the danger of choking. For operations it is recommended to give the initial dose 4 to 8 hours before surgery, as, because of the outflow into the extravasal space, initially a relatively more rapid drop in the factor

Table 3. Dosage guidelines for substitution therapy in hemophilia A and B and von Willebrand-Jürgens syndrome (Landbeck, Kurme, 1972)

Location of bleeding	Factor level required	Duration of treatment
Bleeding into joints, especially knee joint	10–20%	2 days
Muscle bleeding and extensive or threatening tissue bleeding	10–20%	2–3 days
Bleeding in the iliopsoas muscle and calf and under-arm musculature (carpal tunnel syndrome)	30%	3–5 days
Bleeding in the mouth cavity, tooth extraction, minor surgery	30%	5 days
Intracranial, intrathoracic and gastrointestinal bleeding Fractures	30–50%	4–14 days (until the tissue is healed)
Major operations	over 50%	2–3 weeks (until the wound is completely healed)

Table 4. Treatment principles for hemophilia and tooth extraction (Deutsch, 1973, VII)

Severity of hemophilia (F. VIII, IX%)	Number of teeth extracted	Hospitalization	Substitution	Duration (days)	Antifibrinolytics
> 10%	1–(2)	no	no		yes
3–10%	1–(2)	yes	no		yes
under 3%	1–2	yes	yes	2–3	yes
3–10%	> 2	yes	yes	2–5	yes
under 3%	> 2	yes	yes	5–10	yes

follows, and in some circumstances adequate hemostasis is not carried out during the operation. In more extensive interventions the half-life is reduced by the increased turnover of coagulation factors, so that, to keep the necessary level, further injections may be required as early as 2 to 6 hours later.

In mild forms of hemophilia and minor bleeding or operations, factor VIII activity, factor VIII-associated antigen and the von Willebrand factor can be raised to 2 or 3 times the norm by Desmopressin (DDAVP, Minirin). The initial dose of 0.4 to 0.6 μg of Desmopressin per kg of body weight is infused in 20 mins. Further infusions follow every 8 to 12 hours. In hemophilia with an inhibitor and a low and nonincreasing inhibitor titer, adequate hemostasis can be obtained by large quantities of human factor VIII. For higher titers of inhibitors, rising under treatment, alternative methods of treatment are possible. Initially high concentrations of human factor VIII are given, then after a few days this is changed to activated prothrombin complex preparations (FEIBA, Autoplex, Konyne). Alternatively factor VIII from the pig can be used. As this is a foreign protein with antigenic effect, the action ceases after 8 to 10 days. If the initial inhibitor titer is high, the use of activated prothrombin complex preparations is first considered. Alternatively, after plasmapheresis factor VIII preparations can be tried to eliminate the inhibitor. Table 5 gives a summary of the principles of treatment. Prothrombin complex preparations are given in a dosage of 50 to 100 units per kg of body weight at intervals of 4 to 6 hours, depending on the extent of the bleeding and the clinical effect. In the case of minor injuries in some circumstances 25 to 50 units per kg of body weight are sufficient. Control by coagulation analysis of the shortening of the whole blood coagulation time, the r-time in the TEG and the activated partial thromboplastin time follows. However, the coagulation analysis values correlate badly with the clinical effect. By continuous combined doses of factor VIII concentrates and activated prothrombin complex (FEIBA) for several months, the inhibitor was removed, the factor VIII applied had reached its normal half-life, and even after treatment had ceased, the inhibitor was not observed to increase again. Inhibitors of factor IX can be treated with large doses of factor IX concentrates and prothrombin complex preparations, preferably in activated form. We have still insufficent experience. Cytostatics (cyclophosphamide, azathioprine, 6-mercaptopurine) have been used repeatedly, but not with convincing success, to suppress the formation of the inhibitor.

There is a factor VIII preparation and a prothrombin complex preparation available, with which the risk of transmission of hepatitis or AIDS (aquired immuno-deticiency syndrome) is said to be removed. The hepatitis virus and AIDS virus (HTLV III, HIV 1) are said to be

Table 5. Principles of treatment for inhibitor hemophilia A. BU = Bethesda unit, APCC = activated prothrombin complex concentrate (Lechner, 1982)

Present antibody titre	Increase in antibodies after receiving F VIII	Slight to moderate bleeding	Severe to dangerous bleeding Operation
low (< 10 BU/ml)	slight to none (low responder) (< 10 BU/ml)	Human factor VIII (higher dose)	Human factor VIII
low (< 20 BU/ml)	high responder (maximum < 1000 BU/ml)	APCC	First human factor VIII (if nec. after plasmapheresis) after increase in antibodies, APCC or pig AHG
low (< 20 BU/ml)	high responder (maximum > 1000 BU/ml)	APCC (with caution because of possible increase in antibodies)	First human factor VIII (if nec. after plasmapheresis), then APCC
Moderately high (20–100 BU/ml)	high responder	APCC	Plasmapheresis, then human or pig AHG or APCC (if no increase with F VIII concentrate)
high (> 100 BU/ml)	high responder	APCC	APCC

inactivated either by heat treatment (factor VIII preparations, Behringwerke, Hyland, Immuno) or by cold sterilization treatment with β propiolactone and UV irradiation (prothrombin complex preparation, Biotest).

Autosomal Recessive Group

Definition and Pathogenesis

Deficiency in factors II, V, VII, X, XI, XII and XIII, and afibrinogenemia, are inherited through an autosomal recessive gene

(Table 2). These defects are rare. Between 50 and 150 cases of each defect are to be found in the literature. In the case of deficiency in factors V, VII, XI, XII, XIII and afibrinogenemia, there is a true quantitive formation disorder. In the case of deficiency in factor II and factor X, besides absolute deficiency, in some cases a malformed protein with reduced activity, yet immunologically demonstrable, is found. Factors X, V and II lie in the common end-section of the extrinsic and intrinsic paths of coagulation. Complete lack of these factors could be accompanied by a propensity to bleed which is not compatible with life, and is in fact a lethal factor. This becomes probable because in all cases of deficiency a factor activity of at least 1% was demonstrable. In factor VII deficiency partial compensation of the hemostasis mechanism is possible with activation of the prothrombin through the intrinsic system. Conversely, in factor XI deficiency compensation may occur through the intact extrinsic system. In factor XII deficiency there in no clinically evident propensity to bleed. Both sexes are affected by hemostasis disorders of the autosomal recessive group. They appear only in homozygotes. Heterozygotes have a reduction, varying in extent, in the activity of the corresponding factor.

Clinical Approach, Diagnosis and Therapy

Factor II Deficiency (Hypoprothrombinemia). Up to the present, patients from 26 families have been described. The first manifestation is often bleeding from the cord in newborn babies. Bleeding from the mucous membranes (epistaxis, gastrointestinal bleeding, hematuria) is observed. Bleeding of the hemophilic type occurs, with hemorrhage in the musculature and joints. Cerebral bleeding occurs. Menorrhagia is observed in women. There seems to be no clear relationship between the extent of hypoprothrombinemia in the plasma and the degree of tendency to bleed. The most severe cases had a prothrombin concentration of 1% in the plasma. In people who were assumed to be heterozygotes, the prothrombin activity was between 49 and 75%. Heterozygotes show no pathological changes in the global coagulation tests. Only the factor activity is reduced. Homozygotes, with their corresponding distinctly lower prothrombin activity, show varying degreees of prolongation of the partial thromboplastin time, and lowering of the Quick value. The thrombin time is normal. The bleeding time is not, or not substantially, prolonged. Prothrombin complex

preparations are used for substitution therapy. The initial dose is 20 to 25 units per kg of body weight. Alternatively fresh blood, fresh plasma and fresh frozen plasma may be considered. The therapeutic effect of substitution apparently lasts longer than one would expect from the survival time of factor II in the plasma. The defect in hemostasis can be compensated by daily doses of about 500 units or 250 to 500 ml of fresh plasma. The hemostatically adequate concentration is probably at 40% prothrombin activity. Doses of vitamin K are ineffective.

Dysprothrombinemia. Besides the 24 cases of hypoprothrombinemia described up to 1978, in which a prothrombin deficiency can be demonstrated by either immunological or functional methods, up to now 9 cases or families have been described in which dysprothrombinemia was diagnosed. Whereas immunological methods in these cases showed normal or almost normal amounts of prothrombin, with 1 or 2 stage coagulation analysis tests using various snake venoms reduced values were found in varying degrees. There is as yet no biochemical characterization of the defect. There is a hemorrhagic diathesis with bleeding of the skin and mucous membranes, menorrhagia and postoperative bleeding. Muscle bleeding has been described. Hemarthrosis seems not to occur. Heterozygotic individuals are symptom free or have only a mild tendency to bleed.

Factor V Deficiency (Hypoproaccelerinemia, Parahemophilia). Factor V deficiency happens about once in 1 million births. In homozygotes factor V is not below 2%. Heterozygotes have a factor V deficiency of between 45 and 65%. If the activity is above 5 to 10%, adequate hemostasis appears to be ensured. Factor V deficiency does not correlate in every case with the severity of the propensity to bleed. Factor V deficiency appears not to protect from thrombotic complications. Bleeding from the mucous membranes (epistaxis, gingival bleeding) and from the skin are observed. Cerebral bleeding and hematuria are rare. Menorrhagia is observed. Depending on the factor V deficiency, a prolonged partial thromboplastin time and lowered Quick value may be found. Thrombin time and bleeding time are normal. Determination of factor V indicates the degree of the defect. Compensation of the hemostasis can be obtained with at least 500 ml of fresh plasma or fresh-frozen plasma, or 1000 ml of fresh blood. Further substitution should follow at 12-hour intervals. For surgical operations and major bleeding, a factor activity of 30% should be aimed at.

Factor VII Deficiency (Hypoproconvertinemia). Factor VII deficiency occurs about once in 400000–500000 births. Bleeding is observed soon after birth from the umbilical cord and the intestines. In childhood and youth there is posttraumatic bleeding, epistaxis, bleeding into the joints, and menorrhagia in women. Although this is a defect in the extrinsic system, the type of bleeding is often similar to that of hemophilia A or B. Heterozygotes bleed rarely or not at all. There is a lowered Quick value. Partial thromboplastin time, thrombin time and bleeding time are normal. Factor VII activity is lowered according to the degree of severity. Thromboembolic complications can occur in factor VII deficiency. For treatment prothrombin complex preparations are used. Alternatively fresh blood and fresh plasma can be considered. The half-life of factor VII, at 5 hours, is very short. The therapeutic effect of a plasma transfusion lasts longer than one would expect from the lifetime of factor VII. To ensure prophylaxis a factor activity of 10 to 15% of the norm is necessary. Perioperatively, activity of at least 20 to 30% of the norm should be aimed at. Post-operative substitution should last at least 7 to 10 days. Daily doses of 500 to 1000 units of prothrombin complex preparation or 500 ml of fresh plasma are sufficient.

Factor X Deficiency (Stuart-Prower Factor Deficiency). The homozygous form of factor X deficiency occurs about once in 400000 to 500000 births; the heterozygous form appears about once in 500 persons. In homozygotes factor X activity of 1% is found. Heterozygotes, who are phenotypically healthy, have a reduction of factor X to 20 to 25% of the norm. Due to its situation in the course of coagulation, both the extrinsic and intrinsic systems are affected by factor X deficiency. The tendency to bleed may appear soon after birth, but is manifested more often in later periods of life. There is bleeding from the mucous membranes and also hemorrhages similar to hemophilia. Epistaxis, gastrointestinal bleeding, hematuria, skin and deep muscle hematomas, bleeding into the joints and bleeding after injuries occur. With factor X activity below 10%, a hemorrhagic diathesis is to be expected.
The partial thromboplastin time is prolonged, the Quick value is lowered. The thrombin time and bleeding time are normal. The individual determination of factor X gives information on the exact degree of severity of the deficiency.

PPSP preparations and factor X concentrates are the best drugs to choose. As factor X is stable in storage and is also present in serum, older whole blood, plasma and serum can be used besides fresh plasma to relieve bleeding. To compensate for the defect, the activity in the plasma should be 20 to 30% of the norm. Here too the therapeutic effect lasts longer than would be expected from the lifetime of factor X. A daily dose of 500 units of PPSP or 500 ml of plasma appears to be sufficient.

Factor XI Deficiency (Plasma Thromboplastin Antecedent (PTA) Deficiency). A definite coagulation disorder appears in homozygotes with factor XI values below 20%. About 200 case histories exist. Heterozygotes have plasma activity between 30 and 65%. The hemorrhagic diathesis is generally mild. Spontaneous bleeding is rare. Later bleeding, with a certain delay, has been observed after operations. Hypermenorrhoea is rare. There is no certain correlation between factor XI deficiency and hemorrhagic diathesis. Even with low concentrations of factor XI the tendency to bleed may be slight, but postoperative bleeding has been described even with activity up to 50%. The partial thromboplastin time is prolonged, and the Quick value, thrombin time and bleeding time are normal.
For treatment fresh blood, fresh plasma and fresh-frozen plasma are used. As factor XI is stable in storage, older plasma can also be used. To maintain a hemostatically adequate factor concentration, a daily dose of 300 to 500 ml of plasma is sufficient.

Factor XII Deficiency (Hageman Factor Deficiency). Factor XII plays a central part in the system of coagulation, fibrinolysis, kallikrein, kinin and complement. In a deficiency which has been described in over 100 cases, there has been no hemorrhagic diathesis. Thromboembolisms may occur. Hageman, after whom the defect is named, died of a pulmonary embolism. Diminished factor activities of 3 to 5% and even less then 0.2% have been described.
The partial thromboplastin time is prolonged. Quick value, thrombin time and bleeding time are normal. Treatment is not required. Activation of the intrinsic system appears to follow to a sufficient extent from factor XI.

Fletcher Factor, Fitzgerald Factor and Passovoy Factor Deficiency. Up to the present only isolated cases of these factor deficiencies have been described.

Fletcher factor is identical to prekallikrein. The heredity is autosomal recessive. There is no propensity to bleed. The partial thromboplastin time is prolonged. Quick value, thrombin time and bleeding time are normal. The prekallikrein level is lowered by functional as well as by immunological methods.
Fitzgerald factor is identical to high molecular weight kininogen (HMW kininogen). Here also there is no tendency to bleed. The heredity is autosomal recessive. The partial thromboplastin time is prolonged. Quick value, thrombin time and bleeding time are normal.
Williams factor deficiency and Flaujeac factor deficiency are identical to Fitzgerald factor deficiency. Families with the same coagulation defect were described independently of each other.
Passovoy factor deficiency, unlike the factor deficiencies previously described, is inherited through an autosomal dominant gene. There is a propensity to bleed. After operations there may be serious bleeding. Fresh plasma transfusions are necessary before and after operations. The partial thromboplastin time is prolonged. Quick value, thrombin time and bleeding time are normal. The defect may be connected with factor XI deficiency.

Factor XIII Deficiency (Fibrin Stabilizing Factor Deficiency). Factor XIII deficiency is rare; there are reports of about 70 cases. Factor XIII is reduced in both the plasma and the thrombocytes. Factor XIII in the plasma consists of two a-chains and two b-chains; in the thrombocytes only the a-chains are present. The a-chains are functionally active under the influence of thrombin, and cause the covalent cross-linking of the fibrin molecules. In homozygotes factor XIII is reduced to 1% and below. In heterozygotes activity is between 40 and 45%. In the newborn there is almost regularly prolonged bleeding from the stump of the umbilical cord. The propensity to bleed is characterized by ecchymosis, hematomas, and prolonged bleeding after injuries. Intercranial bleeding is comparatively frequent. After operations bleeding often does not begin until 2 to 3 days afterwards. Often, however, it begins immediately. Healing of the wound is delayed by the formation of keloids.

Blood clots are soluble in 5 M urea and 2% monochloracetic acid. Individual determination of factor XIII gives the exact extent of the defect. Partial thromboplastin time, Quick value, thrombin time and bleeding time are normal. For substitution therapy only small amounts

of factor XIII concentrate or plasma are needed, as the half-life of factor XIII is relatively long, and the hemostatic minimum concentration of 5 to 10% is sufficient. The hemostatic effect after substitution lasts longer than would be expected from the lifetime of factor XIII. 500 units of factor XIII or 500 ml of fresh plasma at intervals of a few days up to 2 to 4 weeks are sufficient.

Afibrinogenemia. About 150 cases have been described in world literature. Homozygotes show a hemorrhagic diathesis. Fibrinogen is undetectable or demonstrable with sensitive immunological methods at 5 mg/100 ml. Heterozygotes have hypofibrinogenemia of various degrees. Tendency to bleed does not as a rule occur. 50 to 80 mg of fibrinogen to 100 ml of plasma are sufficient for an adequate hemostasis. The thrombocytes show a functional defect including reduced aggregation with ADP, collagen, adrenalin and thrombin. This can be corrected by the addition of fibrinogen. The expectation of life of homozygous patients is not high. The hemorrhagic diathesis is recognized in the first days of life through bleeding from the stump of the unbilical cord, hematomas, hematemesis and melena. It resembles hemophilia and lasts all through life. Epistaxis, hematuria, gastrointestinal bleeding and, relatively often, cerebral bleeding occur. Menorrhagia is observed.
The blood is uncoagulable. All functional coagulation tests aimed at finding the point in time when a clot is formed from the patient's own fibrinogen show a pathological result. Partial thromboplastin time and thrombin time are infinitely prolonged, and the Quick value is 0. The Thrombotest, Normotest and Hepatoquick have a normal result due to the addition of fibrinogen to the test system. The bleeding time is prolonged moderately to not at all.

As we have said, with either functional or immunological methods little or no fibrinogen can be demonstrated. This is important in reaching a differential diagnosis from dysfibrinogenemia. Here, apart from cases with hypodysfibrinogenemia, there is a normal fibrinogen level with immunological methods and a low fibrinogen level with functional methods. In hypofibrinogenemia there is a reduction of the fibrinogen concentration to about 50 mg%, otherwise results of tests are largely normal. Before surgical operations and where there is bleeding, a minimum fibrinogen level of 50 to 100 mg% is to be aimed at. Substitution is to be carried out with fibrinogen preparations, Cohn

fraction I, cryoprecipitates or plasma. Because of the long half-life of fibrinogen, a repetition of the substitution with long intervals of time is sufficient. The therapeutic effect of a single dose has been observed for several weeks. If the fibrinogen level is raised too sharply, thrombosis is possible.

Combined Factor Deficiency. Individual cases have been described in which there was a combined deficiency in factor V, factor VIII and the factors of the prothrombin complex, as well as combined deficiencies in factors VII and VIII, VIII and IX, VIII and XI, and also in factors VIII and IX together with a platelet defect. The so-called Dynia defect comprises an abnormality of the endogenous coagulation system, based on impaired interaction between factor IXa and factor VIII with limited activity of factor X. The pattern of heredity is not clear.

Autosomal Dominant Group

Dysfibrinogenemia. About 88 patients and their families with dysfibrinogenemia have been described in world literature. The fibrinogen molecule is malformed. In heterozygotes there is a mixture of normal and defective fibrinogen, while homozygotes have only defective fibrinogen. Since the amino acid sequence of fibrinogen has now been completely analyzed, the altered amino acid synthesis of dysfibrinogens has now been explained in a large number of cases. As far as we know up to the present, only single amino acids at the end of single fibrinogen chains are responsible for the sometimes marked functional changes in dysfibrinogens. In the fibrinogen "Detroit", for example, the amino acid serine is exchanged for arginine in position 19 counted from the N-terminal end of the alpha chain (Fig. 1/I). Fibrinogen "Paris I" has a lengthened gamma chain at the C-terminal end with an increase of 2500 in the molecular weight. The dysfibrinogen is restricted in its function. The formation of a clot is thus delayed. Corresponding to the phases of the fibrinogen-fibrin-conversion there is in some cases a delay in the fibrinopeptide split-off, and more frequently a delay in the aggregation of the fibrin monomers to polymers. In rare cases there is a defect of cross-linking through factor XIII. A combination of defects can occur in one patient.
A hemorrhagic diathesis is observed in only about 50% of patients. The tendency to bleed does not appear until adolescence, and is often

only moderately pronounced. Increased bleeding after injuries and operations and a tendency towards dehiscence of wounds are observed. Thromboembolic complications occur despite delayed blood clotting even without substitution. The diagnosis is most often made by chance at a routine coagulation analysis.
Corresponding to the extent of the functional disturbance of the fibrinogen molecule there is a prolongation of the partial thromboplastin time, the thrombin time, and the reptilase time, and a lowering of the Quick value. Determination of fibrinogen by functional methods (measuring of coagulation time, determination of coagulable protein, nephelometry) give low values in comparison with immunological determination methods, which give high or normal values. Hypodysfibrinogenemia has been described.
Substitution treatment with fibrinogen, Cohn fraction I, or cryoprecipitate is in most cases not required. In patients with a hemorrhagic diathesis, posttraumatic and perioperative substitution with relatively small quantities of fibrinogen is necessary. 1 to 2 gr of fibrinogen is sufficient for compensation of hemostasis.

Von Willebrand-Jürgens Syndrome

Definition and Pathogenesis

The von Willebrand-Jürgens syndrome is a hemorrhagic diathesis inherited through an autosomal dominant gene. Cases of von Willebrand-Jürgens syndrome with an autosomal recessive heredity have been described. Seven patients have been reported in whom the von Willebrand-Jürgens syndrome has been acquired in the course of life. Most of these patients had disorders of the immune system at the same time. The von Willebrand-Jürgens syndrome is relatively common. There are no exact figures; it is considered that there is one such patient to 2 or 3 hemophiliacs. The disease is characterized by prolonged bleeding time, normal thrombocyte count and a deficiency of factor VIII. The latter is qualitatively different from the factor VIII deficiency in hemophilia A. The majority are deficient in factor VIII; factor IX deficiency is rare. The factor VIII molecule consists of two components, the low molecular weight component (molecular weight 100000 to 200000) carrying the coagulative activity, and the high molecular weight component (molecular weight 1000000 and above) representing the so-called factor VIII antigen, the von Willebrand

factor and the ristocetin cofactor. The last three functions are attributed to the same molecule. The von Willebrand factor ensures that the thrombocytes adhere to the subendothelium, and is necessary for primary hemostasis. Patients with the von Willebrand-Jürgens syndrome show both a reduction of factor VIII activity and, to about the same extent, a decrease in factor VIII antigen which can be preciptated with heterologous antibodies. Homozygotes have a reduction to 15 to 50% of the norm (normal range 60% to 100%). This results in the combination of plasmatic and thrombocytic coagulation defects. The thrombocytes are normal in themselves, but restricted in their function by lack of the necessary plasmatic cofactor.

Clinical Findings and Diagnosis

Hemorrhagic diathesis manifests itself in early childhood and decreases in intensity in the course of life. Bleeding from skin and mucous membranes, epistaxis, gastrointestinal bleeding and menorrhagia are observed, as well as bleeding after tooth extraction and operations. Petechiae are rather rare. Post partum bleeding and hemarthrosis are not regularly observed.

The partial thromboplastin time is prolonged. Quick value, thrombin time and platelet count are normal. Bleeding time is prolonged. In mild forms of the von Willebrand-Jürgens syndrome, and under treatment, normal bleeding times have been observed with Duke's method, whereas the bleeding time according to Ivy and according to Mielke is prolonged. In borderline bleeding times the aspirin tolerance test may be of help. About 2 hours after 0.6 gr of acetyl salicylic acid (aspirin) has been given orally, a distinct prolongation of the bleeding time, exceeding the normal extent, is observed. The ristocetin-induced thrombocyte aggregation is inhibited. The aggregation to collagen, ADP, and adrenalin is normal (Fig. 1/VI). This enables it to be differentiated from drug-induced and other disturbances of thrombocyte function, in which the aggregation to ristocetin is normal, but to other stimulants is restricted. The aggregation to ristocetin is normalized by the addition of normal plasma or cryoprecipitate. This is not the case in the Bernard-Soulier syndrome, in which the defect is thrombocyte-related, but otherwise shows an aggregation pattern similar to that of the von Willebrand-Jürgens syndrome. The procoagulative activity of factor VIII, and also the immunologically demon-

strable factor VIII antigen, are lowered. This can be used to arrive at a differential diagnosis from hemophilia A, in which the factor VIII-associated antigen lies within normal limits. The platelet adhesion is reduced. There are variants of the von Willebrand syndrome which deviate from the typical picture in one or more characteristic features. Thus there are forms in which the factor VIII-associated antigen is normal, but which nevertheless have a prolonged bleeding time and a limited ristocetin-induced platelet aggregation, and others in which the factor VIII activity is normal, and the factor VIII-associated antigen and von Willebrand activity are reduced; and there are patients in whom only the von Willebrand activity or ristocetin cofactor activity is reduced.

Treatment

The defect in the von Willebrand-Jürgens syndrome is localized in the larger component of the factor VIII molecule. All blood fractions containing this component are therapeutically useful. We can consider fresh-frozen plasma, cryoprecipitate, Cohn's fraction I-O and to a certain extent also factor VIII concentrates. Highly purified factor VIII is ineffective. Hemophilia A plasma can also in principle be used. The associated antigen of the factor VIII molecule is capable of producing an increase in the procoagulative activity of factor VIII. After substitution, unlike hemophilia A, factor VIII activity in severe cases rises considerably within 4 to 8 hours, and in less serious cases within 12 to 18 hours. The rise in the procoagulant activity of factor VIII is higher than would be expected from the quantity of factor VIII given. Equally, the compensating effect on the propensity to bleed and the parameters of coagulation analysis is longer than might be assumed from the lifetime of factor VIII. In the case of a hemorrhage or an imminent operation, it is recommended to give initially 5 ml per kg body weight of fresh plasma, and 5 ml per kg of body weight every 24 to 48 hours. Corresponding quantities of the other plasma fractions are to be used. The hemorrhagic diathesis decreases and all parameters of coagulation analysis become normal. Ivy's bleeding time is still partly pathological when Duke's bleeding time is already normal. Highly purified factor VIII preparations normalize factor VIII activity, but not the thrombocyte defect. DDAVP (Minirin) also corrects the hemostatic defect, raising factor VIII activity and factor VIII antigen.

Acquired Abnormalities of Synthesis

Prothrombin Complex Deficiency in the Newborn

Definition and Pathogenesis

The reduction of the factors of the prothrombin complex II, VII, IX and X, is predominantly the result of a vitamin K deficiency. It is caused by

1. absence of vitamin K reserves
2. inadequate vitamin K intake
3. absence of vitamin K synthesis because the intestinal flora is still lacking
4. increased need of vitamin K
5. inadequate synthesis by the immature liver cells.

Clinical Findings and Diagnosis

In the first days after birth the factors of the prothrombin complex are usually low, lying between 30 and 50% of the norm. A hemorrhagic diathesis due to a prothrombin complex deficiency occurs in about 0.1 to 1% of newborn babies. The propensity to bleed shows within 2 to 5 days after birth, during which there is a further loss of the activity of the factors. In the following days and weeks the coagulation defect normalizes. In premature babies the coagulation defect is more marked. The hemorrhagic diathesis appears in bleeding from the navel and from the mucous membranes, hematomas and gastrointestinal bleeding.

The diagnosis is reached through the lowered Quick value. The partial thromboplastin time and thrombin time are often prolonged, caused by restriction of the function of the newborn child's fibrinogen, with a polymerization disorder which, clinically and in coagulation analysis, resembles dysfibrinogenemia. As synthesis in the liver increases, the fetal fibrinogen occurring physiologically is replaced by fibrinogen which is fully functional. A differential diagnosis should distinguish all congenital hemorrhagic diatheses.

Treatment

In mild to moderately severe cases 1 to 2 mg of vitamin K given parenterally, is enough to raise the Quick value considerably within

the following 8 to 24 hours. Normalization does not occur because of the liver's limited synthetic capacity. Repeated doses of vitamin K at intervals of 1 to 2 days are as a rule necessary. In severe cases in which immediate hemostatic compensation is needed, prothrombin complex preparations or fresh plasma and even plasma which has been stored for a short time can be used.

Disturbances in Absorption and Utilization of vitamin K in Adults

Definition, Pathogenesis, Clinical Findings and Diagnosis

The vitamin K deficiency syndrome with reduction in the factors of the prothrombin complex has the following causes:

1. Failure to absorb vitamin K with the food. This occurs only with long-term parenteral feeding, and through the destruction of the intestinal flora which synthesizes vitamin K, owing to long-term treatment with antibiotics.
2. Reduced vitamin K absorption due to absence of the flow of bile in the intestine, and in cases of the malabsorption syndrome. In cases of blockage of the bile duct with liver function intact, the Quick value falls to about 40%. Malabsorption syndromes are caused by sprue, pancreatic insufficiency, gastrointestinal fistulas and enterocolitis.
3. Disturbances in the utilization of vitamin K due to liver cell damage such as hepatitis, cirrhosis of the liver, hemochromatosis, Wilson's disease and acute toxic liver damage in amanita poisoning and carbon tetrachloride poisoning. The hemostatic defect is complex and is dealt with in detail elsewhere. A hemorrhagic diathesis occurs if the Quick value is around and below 15%. The type of bleeding is that described in cases of deficiency of the individual factors of the prothrombin complex. In liver cell damage the propensity to bleed and the type of bleeding are modified by a facultative increase in the turnover of coagulation and fibrinolysis as well as thrombopenia.

The Quick value is lowered, and partial thromboplastin time, thrombin time and bleeding time are normal. In hemorrhagic diatheses caused by liver cell damage the coagulation analysis is altered according to the additional defects.

Treatment

Parenteral administration of 1 mg of a water-soluble vitamin K preparation makes the Quick value rise by 15 to 30% within a day. 10 mg to 20 mg of vitamin K given parenterally shows an effect after 4 to 6 hours and normalizes the Quick value in 8 to 24 hours. In the case of liver cell damage vitamin K has little or no effect, but it should be tried in every case.

Reduction in Prothrombin Complex through Antibiotics

Hypothrombinemias with a fall in the Quick value may occur during therapy with beta-lactam antibiotics which have an N-methylthiotetrazole (NMTT) side chain in the molecule (e.g. latamoxef, cefamandol, cefoperazone, cefmenoxime). The NMTT which is split in the body inhibits the epoxide reductase of the vitamin K-cycle. The regeneration of vitamin K is reduced and interrupted. The mechanism of action corresponds to that of the coumarins (Fig. 1). The carboxylation of the glutamic acids of the prothrombin complex precursors is restricted. The acarboxy precursors can be demonstrated in the plasma (PIVKA). They cannot be activated.

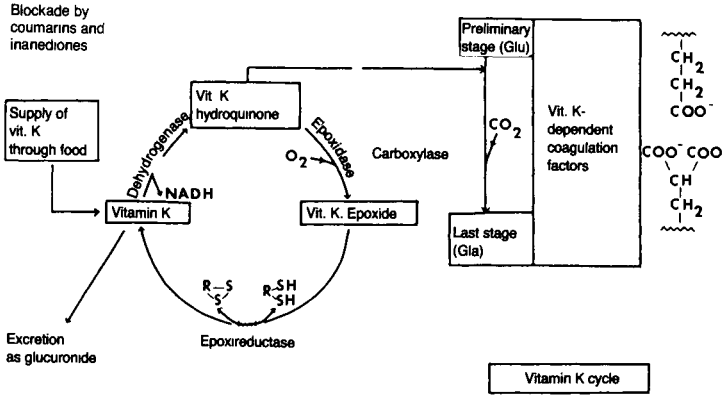


Fig. 1. Action mechanism of the inhibition of the coagulation factors of the prothrombin complex by coumarin and indandione through the interruption of the vitamin K regeneration cycle (Weber et al. 1981, XIII)

A fall in the Quick value preferentially occurs under the following conditions: in patients of advanced age, in malnutrition, in prolonged parenteral nutrition without vitamin K substitution, in sepsis, after trauma and surgery, in advanced liver disease and cholestasis, renal insufficiency and during therapeutic anticoagulation with coumarin derivatives. In the situations mentioned a latent vitamin K deficiency, a disorder of vitamin K utilization and/or delayed renal elimination of the antibiotic is to be assumed or is present. In these cases without vitamin K substitution, hypothrombinemias occur in 30% to 65% of the patients under beta-lactam antibiotics with an NMTT side chain, especially with a high dose of antibiotic. Even with the use of beta-lactam antibiotics without an NMTT side chain, hypoprothrombinemias have been observed in up to 20% of cases for reasons which are not absolutely clear. The critical fall in the Quick value develops about 3–8 days after the start of the antibiotic therapy. 5 to 10 mg of vitamin K_1 given intravenously brings the Quick value back into the normal range within 12 to 36 hours. The prophylactic administration of ca. 10 mg vitamin K_1/week prevents the coagulation disorder. The daily vitamin K_1 requirement of healthy subjects is assumed to be 75 to 150 μg/day. The normal plasma concentration of vitamin K_1 lies at 1 to 2 ng/ml.

Anticoagulant Treatment with Coumarin Derivatives

Definition and Genesis

Coumarin derivatives (Marcumar, Sintrom, Tromexan, Coumadin) are vitamin K antagonists. They inhibit the post ribosomal completion of the prothrombin complex molecule (Fig. 1; cf. Fig. 3, I). The amounts of the factors synthesized in the absence of vitamin K are indicated by PIVKA II, VII, IX and X (protein induced by vitamin K absence) and, measured by immunological methods, exist in normal concentrations. Owing to the absence of the molecular components necessary for calcium binding and thus for the activity of the prothrombin complex factors, functional tests measure low activity, which is responsible for the hemostatic defect. After taking coumarin derivatives, after a latency period of 6 hours there is a continuous drop in the factors, which is complete on the 2nd to the 3rd day after the dose. The therapeutic area varies according to the test system used (Quick value

15–25%, Thrombotest 5 to 15%, Hepato-Quick 10 to 20%). Overdose gives rise to hemorrhagic diathesis which is described elsewhere, and which is accompanied by bleeding from the skin, mucous membranes and soft tissues, and by hematuria, epistaxis, bleeding from the gums and gastrointestinal bleeding. Rarely, there is intramural intestinal bleeding, bleeding in the ovary and retroperitoneal hematoma. In isolated cases there is resistance to coumarin. Many drugs influence the action of coumarin. The possibilities of interaction are described elsewhere. For overdose it is sufficient to give 1 to 5 mg of vitamin K (Konakion) orally in a single dose. For severe hemorrhages immediate substitution with prothrombin complex preparations may be nesessary. A dose of 10 to 20 mg of vitamin K causes the Quick value to rise within 8 to 12 hours in an area in which adequate hemostasis has been ensured. The duration of the effect of coumarin derivatives, demonstrable by means of the thromboplastin time, is about 10 to 14 days after discontinuation of the drug with phenprocoumon (Marcumar), and 4 to 8 days with acenocoumarol (Sintrom). The hemostatic defect is removed at an earlier point, before reaching the normal thromboplastin time.

Turnover Disorders

Consumption Coagulopathy, Disseminated Intravascular Coagulation and Fibrinolysis

Definition and Pathogenesis

The terms "consumption coagulopathy" (Lasch, 1961, 1967), "disseminated intravascular coagulation" (McKay, 1966) and "thrombohemorrhagic syndrome" (Selye, 1966) are used to describe phenomena which are observed in the course of a generalized, more rarely localized and progressive activation of the coagulation system which occurs in the circulation (Fig. 2).
The term "consumption coagulopathy" puts the emphasis on the increasing turnover of plasmatic coagulation factors and of the thrombocytes, which, after a phase of hypercoagulability of the blood with the hemostasis potential increasingly being used up, develops into

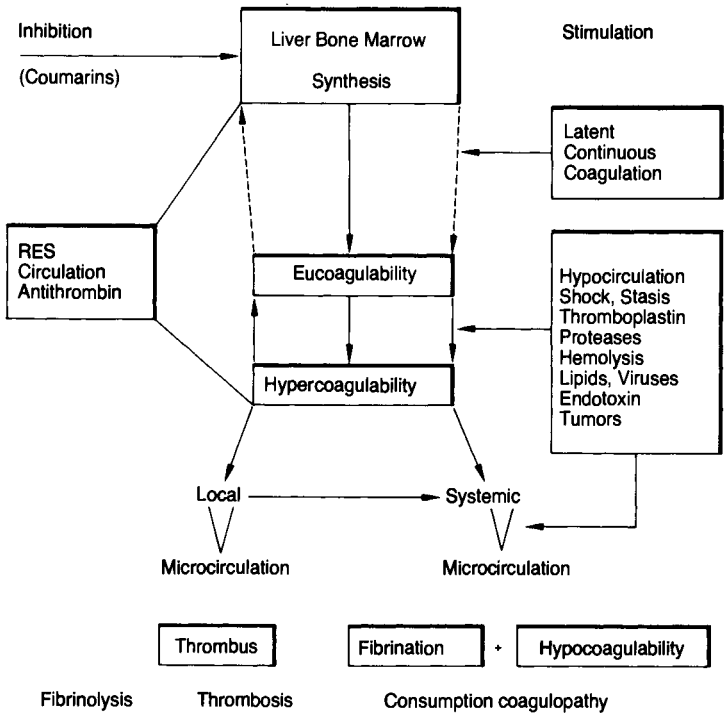


Fig. 2. The dynamic balance of hemostasis, and ways in which it can be influenced by exogenous and endogenous factors

a hypocoagulability resulting in hemorrhagic diathesis. A secondary activation of the fibrinolysis, which may sometimes occur, leads to the further consumption of coagulation factors and potentiates the hemorrhagic diathesis. The term "disseminated intravascular coagulation" (DIC) places the emphasis on the morphological substrate, the microthrombi in the peripheral vessels of numerous organs. The "thrombohemorrhagic-syndrome" describes the coexistence of thrombosis and hemorrhage. The syndromes are acquired hemorrhagic diatheses. The coagulopathies caused by the disorders of turnover are not independent diseases but instead occur as the secondary phenomena of primary diseases. Consumption coagulopathies and hyperfibrinolyses

frequently occur together, but with a varying intensity depending on the nature and course of the primary disease. This has an influence on the prognosis and treatment. The following combinations seem possible:

1. consumption coagulopathy alone through activation of the coagulation system
2. consumption coagulopathy with slight secondary fibrinolysis
3. consumption coagulopathy with predominant secondary fibrinolysis
4. primary fibrinogenolysis alone
5. defibrination syndrome induced through 1–4.

Consumption coagulopathy as a consequence of the intravascular coagulation process is characterized by exhaustion of the hemostasis potential with a tendency to bleeding and the simultaneous deposition of fibrin thrombi in the micro- and macrocirculation. This leads locally to the development of microcirculatory disorders and systemically to circulatory shock. The hyperfibrinolysis is a consequence of an excessive production of plasmin with the degradation of fibrin, fibrinogen, and of Factors II, V and VIII and the appearance of fibrinogen-fibrin split products which inhibit fibrin polymerization and promote a hemorrhagic diathesis (Table 6).

Table 6. Consequences of consumption coagulopathy

1.	Hemorrhagic diathesis
	Hemostasis potential used up through reduction in the thrombocytic and plasmatic components of the coagulation system.
	Intravascular coagulation with or without fibrin depositions.
	Compensatory increase in fibrinolysis with the development of a combined hemostasis defect
	Defibrination syndrome
2.	Local microcirculation disorder, possibly with necrosis and organ manifestations
	Bilateral renal cortex necrosis – acute renal failure
	Hypophyseal necrosis – Sheehan syndrome
	Adrenal cortex necrosis – Waterhouse-Friderichsen syndrome
	Hepatic necrosis – acute hepatic dystrophy
	Microembolisation of the pulmonary circulation – acute cor pulmonale
3.	Generalized microcirculation disorder
	Irreversible shock

Table 7. Mechanisms precipitating intravasal coagulation and diseases which are frequently associated with a consumption coagulopathy

Mechanism	Syndromes
Endotoxin	Sepsis with gram-negative bacteria Hepatic insufficiency (systemic loading with intestinal endotoxin)
Reduced clearance (circulation disorder) and disordered degradation (RES-damage) of coagulation factors	Shock, Kasabach-Meritt syndrome, giant hemangioma, Aortic aneurysm Liver damage Portal hypertension
(Tissue-)thromboplastin and thromboplastin-like substances; colloidal substances	Tumors Leukemia Hepatic cell necrosis (e. g. bulbous agaric fungus) Multiple trauma Virus infections (endothelial destruction) Septic abortion, retained abortion Amniotic fluid embolism Hemolysis (hemolytic-uremic syndrome, thrombotic-thrombocytopenic purpura) Increase in blood lipids
Proteolytic enzymes	Leukemia Snake poisoning
Foreign surfaces	Extracorporeal circulation
Antigen/antibody complexes	Faulty transfusions Graft rejection

This syndrome occurs in many diseases. The pathogenesis is polymorphous. There is no uniform etiology (Table 7). The increased turnover can take an acute or chronic course with manifest and latent hemorrhagic diathesis. The groups of diseases in which increased turnover has been observed are listed in Table 8.

Disseminated intravascular coagulopathy is caused by sepsis and septic shock in about 40%–60% of cases, by trauma or surgery in 15%–20% of cases, by tumors in 10%–20% of cases, by liver disorders in approximately 10% and by other diseases in up to 20% of cases.

Bleeding occurs to varying degrees in 75%–88% of patients; cutaneous bleeding occurs in about 65% and gastrointestinal bleeding in approximately 50% of these cases. In 40%–90% of patients who die of disseminated intravascular coagulopathy, autopsy findings include microthrombosis in one or more organs, affecting the lungs in 50%–100%, the kidneys in 50%–70% and the skin in about 70% of cases.

Table 8. Syndromes predisposing to the occurrence of acute and chronic forms of an increased turnover of coagulation factors

A. *Acute disorders of turnover*
1. Obstetric complications:
Abruptio placentae, amniotic fluid embolism, retained abortion
2. Septicemias, gram-negative bacteria
Purpura fulminans exanthemat., virus diseases,
Rickettsioses, malaria
3. Various forms of shock, cardiogenic, traumatic, hemorrhagic, endotoxic, septic, anaphylactic, shock due to burns
4. Hemolytic syndromes:
Transfusion reactions
Hemolytic anemias
Hemolytic-uremic syndrome
5. Acute organ necroses:
Acute pancreatitis, acute hepatic cirrhosis
6. Postoperatively after surgery on the lungs, pancreas, liver, heart, prostate, after extracorporeal circulation, after transplants (kidneys, liver)
7. After traumatic processes:
Fat embolism, extensive soft tissue injuries
B. *Chronic forms*
1. In disorders of circulation as a result of abnormal vessel formations or vessel anomalies:
Congenital cyanotic heart defects
Giant hemangioma
Osler's disease
Hepatic cirrhosis with portal decompensation
Portocaval shunt
2. Metastatic carcinomas
Prostatic carcinoma, gastric carcinoma, pancreatic carcinoma, malignant diseases of the hemopoietic system

Intravascular Activation of Coagulation and Fibrinolysis

A precondition for the activation of the coagulation system in vivo is the supply or release of procoagulatory valences. The activation can be set in motion through three mechanisms (Table 7):

1. Direct activation of prothrombin or Factor X through proteolytic enzymes (e.g. snake poison)
2. Activation via the extrinsic system through the inflow of thromboplastic materials into the bloodstream (abruptio placentae, traumatic shock, carcinoma)
3. Activation of the Hageman factor through the intrinsic system (e.g. extracorporeal circulation, subendothelium).

Stroma originating from damaged, hemolysing erythrocytes activates the coagulation via the extrinsic system. Increased turnover of this kind is observed after mechanical erythrocyte damage in the course of extracorporeal circulation, of a microangiopathic-hemolytic syndrome and also after immunologically induced hemolyses in consequence of faulty transfusions. All of the trigger mechanisms for intravascular coagulation induce platelet aggregation with the release of procoagulatory materials. Possible triggers are thrombin, antigen/antibody complexes, collagen, catecholamines and endotoxin. Thrombocytes are not essential for the activation of coagulation, but play a supportive role. Leukocytes contain procoagulatory activities but also proteolytic enzymes. Following the administration of endotoxin there is a fall in the neutrophils in particular, with the release of thromboplastic materials. Consumption coagulopathies are seen fairly frequently in cases of acute leukemia and promyelocytic leukemia. Damage to the vascular endothelium with the exposure of subendothelial structures can induce and maintain a disseminated intravascular coagulation. If the integrity of the vessel is impaired, thromboplastic material is released. Subendothelial structures activate the intrinsic system and the thrombocytes. The production of prostacyclin in the endothelium is reduced. Vessel damage occurs after the action of endotoxins, and in circulatory shock as catecholamine, histamine and serotonin effects. In the intrinsic system Factor XII can induce the activation of the complement cascade. Activated complement components lead to platelet aggregation with release reactions which perpetuate a disseminated intravascular coa-

gulation; they influence the course of a disseminated intravascular coagulation through the vessel permeability, vessel reactivity and chemotaxis. Immune complexes set the coagulation process in motion by several mechanisms. They activate Factor XII, lead to vessel damage, activate the complement system and induce platelet aggregation. In this way they accelerate the increased turnover.
The activation of the fibrinolysis system takes place:

1. directly through specific activators,
2. indirectly as a result of the activation of the coagulation system. The direct activation takes place through the infusion of streptokinase, urokinase and after trauma to organs rich in activators such as the prostate and lungs.

The secondary increase in fibrinolysis can be seen as a compensatory mechanism to prevent the consequences of the intravasal coagulation. Fibrin has a higher affinity to plasminogen and plasminogen activators than fibrinogen and adsorbs these in the course of the disseminated coagulation process. Plasmin formation is made easier through the spatial configuration of the enzymes in the molecule complex. The degradation of circulating fibrin takes place. Precipitated fibrin induces – directly or through local tissue hypoxia – the release of endothelial plasminogen activator, which converts coprecipitated plasminogen into plasmin. A reminder should be given again about the direct activation of fibrinolysis through the Hageman factor (Fig. 9/I). Local decomposition of fibrin depositions takes place with the appearance of fibrin split products in the circulation. A plasminemia only develops if, after reopening of the capillary bloodstream, fibrinolytic activators and plasmin are swept into the circulation. A fibrinolysis accompanied by fibrinogenolysis is observed. In the systemic lysis after generalized exposure to the effects of plasmin, fibrinogenolysis predominates with simultaneous degradation of Factors V and VIII.
The course of a disseminated intravascular coagulation can be modified by various factors. An increasing reduction in the inhibitors of the coagulation factors leads to progression. The most potent inhibitor, antithrombin III, which acts at numerous points in the coagulation system, but preferentially inhibits thrombin and activated Factor X, is increasingly used up in the course of a state of increased turnover. Inadequate activation of the fibrinolytic system through a reduction in the activators and an increase in the inhibitor potential of the fibrinoly-

sis, especially in sepsis, leads to the accumulation of soluble fibrin in the plasma and an impairment of the lysis of microthrombi in the peripheral vascular region. This leads to an increasing disorder of the microcirculation resulting in further organ damage. In the course of an activation of coagulation there is increasing impairment of the clearance capacity of the reticuloendothelial system for activated coagulation factors, fibrin and fibrin split product complexes and also for the substances which trigger a disseminated coagulation such as endotoxins and immune complexes. This further intensifies the turnover disorder, depending on the microcirculation disorder within the organs of the reticuloendothelial system. In a state of shock the stasis within the microcirculation promotes the procoagulatory stimulation in dependence on the disordered hemodynamics and the altered rheological properties of the blood. The microcirculation is also impaired by increases in the coagulation potential such as hyperfibrinogenemia in sepsis.

Clinical Aspects

Increased Turnover in the Coagulation and Fibrinolysis System

In consequence of the procoagulatory stimulation the intravasal action of thrombin leads to the splitting off of the fibrinopeptides A and B from the fibrinogen molecule, and to the activation of the coagulation Factors V, VIII and XIII and of the thrombocytes. At the start of an increase in turnover there is a phase of hypercoagulability, which is of varying duration depending on the acuteness of the process. Clinically this often escapes detection on coagulation analysis. An increasing intravasal accumulation of fibrin monomers occurs, which are described as des-A-fibrin and des-AB-fibrin according to the extent of the fibrinopeptide's-cleavage (Table 9). Up to a certain threshold concentration fibrin monomers and fibrin oligomers remain dissolved in the circulation as fibrin/fibrinogen-complexes and, if fibrinolysis simultaneously takes place, as fibrin/fibrin split product and fibrin/fibrinogen split product complexes. If the procoagulatory stimulation is interrupted either spontaneously or induced through therapeutic measures, the hypercoagulability decreases in dependence on the inhibitor potential available and the extent to which the clearance capacity of the RES is intact, and a state of encoagulability of the blood

Table 9. Possible pathological mechanisms for the formation of fibrinogen derivatives and their detection by coagulation analysis (Heene, 1975a)

Type of turnover disorder	Thrombin-induced derivatives		Plasmin-induced derivatives		
	Fibrin monomers	Fibrin monomer-fibrinogen complexes	Fibrin monomer-split product complexes	Fibrin split products	Fibrinogen split products
Consumption coagulopathy	+	+			
Secondary fibrinolysis			+	+	+
"Primary" fibrinolysis					+
Intravasal mechanism	**Coagulation**		**Fibrinolysis**		**Fibrinogenolysis**
I. Plasma					
Ethanol test	+	+			
Protamine sulfate test	+	+	(+)		
Thrombin time (prolonged)	(+)	(+)	+	+	+
Reptilase time (prolonged)	+	+	+	+	+
II. Serum					
Staph. clump test			+	+	+
Immunological methods			+	+	+

is restored without further consequences for the body. Continuing stimulation leads to a progressive increase in turnover and the consumption of coagulation factors and thrombocytes (Table 6, Fig. 2). Hypocoagulability develops and, in dependence on cardiovascular function, certain localization factors and the extent of the secondary fibrinolysis, fibrin is deposited in the microcirculation and/or in the large venous vessels. Factors I (fibrinogen), V, VIII and the thrombocytes and also to a lesser extent Factors II and X are affected by the consumption. Soluble fibrin circulates in varying amounts which depend on the concentration of the complex partner, fibrinogen, in the circulation. In correspondence with the course taken by the condition, a distinction can be drawn between acute, subacute and chronic disseminated intravascular coagulation (Table 8). The acute form of DIC can lead to the total exhaustion of the hemostasispotential with massive hemorrhagic diathesis. The reduction in the factors is less marked in the subacute form and takes an episodic course, in dependence on the course of the underlying disease, with periods of just a latent tendency to hemorrhage and periods of marked hypocoagulability with manifest hemorrhagic diathesis. The low-grade consumption reaction in chronic DIC can lead, through a compensatory increase in the synthesis of coagulation proteins, to normal or even increased activities of the factors and of the fibrinogen concentration. Where there is locally circumscribed, secondary lysis of fibrin deposits, fibrin split products appear in the circulation. With more marked activation of lysis, plasmin and fibrinolysis activators flow into the circulation and fibrin/fibrinogen split products appear. Because of their ability to form complexes with fibrin, they counteract the development of microthrombosis. The systemic fibrinolysis can become so intensive that complete degradation of fibrinogen and of Factors V and VIII which are similarly sensitive to plasmin, takes place, this aggravating the hypocoagulability.

Fibrin Deposition

Depending on the acuteness of the process and on locally acting factors such as stasis, catecholamine effects, and endothelial fibrinolysis activators, fibrin is deposited in numerous organs, this resulting in a disorder of the microcirculation and damaged organ function or total organ necrosis (Table 6). The organs preferentially affected are the

skin, kidneys, adrenals, liver and lungs. Perifocal necroses and hemorrhages also occur. Macrothromboses in the deep vein system of the legs and the pelvis are similarly often observed. The preferential deposition of fibrin in the renal cortex, which is promoted through localization factors such as catecholamines and corticoids, is the cause of a bilateral renal cortex necrosis with irreversible organ damage. Necrosis of the skin occurs at the acral extremities in particular. The obstruction of the pulmonary bloodstream through fibrin clots is due to the local development of thrombi and to microemboli from the venules of the systemic peripheral vessels. The deposition of fibrin in the pulmonary bloodstream is to be seen as one of the causes of so-called "shock lung". Necroses of the liver lead to acute hepatic dystrophy. Microthrombosis which takes a generalized course can initiate or perpetuate a state of shock through impairment of the nutritive supply of the peripheral vascular region. The deposition of a loose fibrin network in the peripheral vascular region causes a microangiopathic hemolytic anemia with the demonstration of schistocytes. Even though fibrin may not be demonstrated in the microcirculation on pathological-anatomical post mortem, this does not exclude the possibility that microthrombus formation may have taken place during life, because a secondary increase in fibrinolysis may have led to the reopening of the peripheral vascular region.

Hemorrhagic Diathesis

The tendency to hemorrhage, which is defined as "consumption coagulopathy", is a consequence of the progressive fall in the coagulation factors and the secondary fibrinolysis (Table 6). In the majority of cases the hemorrhagic diathesis remains clinically latent. The coagulation defect can then only be objectively demonstrated through coagulation analysis. About one third of patients show a severe tendency to hemorrhage, the remaining two thirds having only a moderate or no manifest hemorrhagic diathesis. The hemorrhagic diathesis occurs in the form of a combined thrombocytic and plasmatic tendency to bleeding. At the skin and mucous membranes petechiae, purpura, but also ecchymoses and suffusions are observed. Hemoptysis, intestinal bleeding from erosions and ulceration of the gastrointestinal tract develop, and also secondary hemorrhage from puncture sites and surgical wounds and central-nervous symptoms through microhemorrhages in the central nervous system. The initial lesions are often

thrombotic occlusions in the microcirculation with tissue damage and necroses, into which bleeding takes place.

Diagnosis

The diagnosis of an increased turnover in the coagulation and/or fibrinolysis system is made on the basis of clinical and coagulation analysis parameters (Tables 6, 9 and 10, Figs. 3 and 4). If a coagulation analysis is carried out just once, only distinct deviations from the norm will indicate a consumption coagulopathy. Since the normal range for many coagulation analysis test systems is relatively broad, in individual cases slight deviations from the individual normal values do not provide any unequivocal information when the increased turnover is just starting or regressing or in the chronic form of disseminated

Table 10. Diagnostic laboratory criteria for consumption coagulopathy and increased secondary fibrinolysis (Heene, 1975a)

Consumption of the components of the hemostasis system induced through:	Analytical Parameters
a) *Action of thrombin*	
Thrombocytopenia	
Reduction in Factors V, (VIII), XIII	Thrombocyte count Determination of Factors V–VIII–XIII
Hypofibrinogenemia	Fibrinogen concentration
Formation of soluble fibrin monomer complexes and fibrin monomer-fibrinogen complexes	Ethanol test
Reduction in antithrombin III	Antithrombin III
b) *Action of thrombin and plasmin*	
Reduction in Factors V and VIII	Determination of Factor V–VIII
Hypofibrinogenemia	Fibrinogen concentration
Formation of uncoagulable fibrinogen/ fibrin split products (FSP) and of their complexes with fibrin monomer	Thrombin and reptilase times Demonstration of FSP in the serum
Reduction in plasminogen	Determination of plasminogen
Increase in the activator activity	Euglobulin lysis time

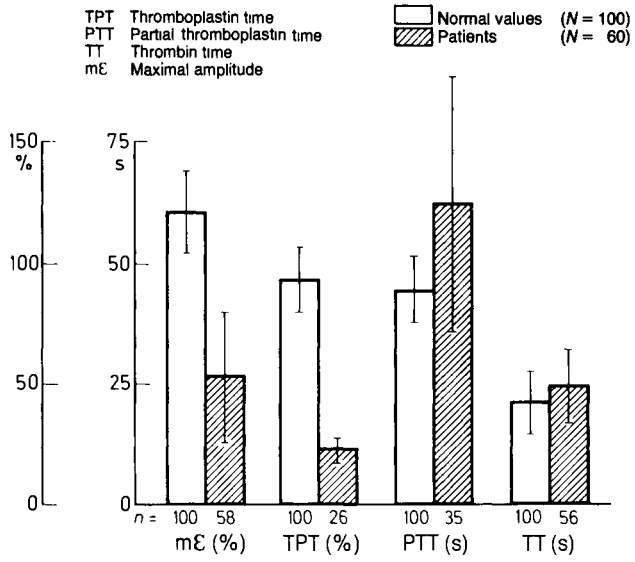


Fig. 3. Diagnosis of consumption coagulopathy by coagulation analysis: mean difference of the values for global and grouptests in 100 normal subjects and a total of 60 patients with consumption coagulopathy (Lasch, 1969)

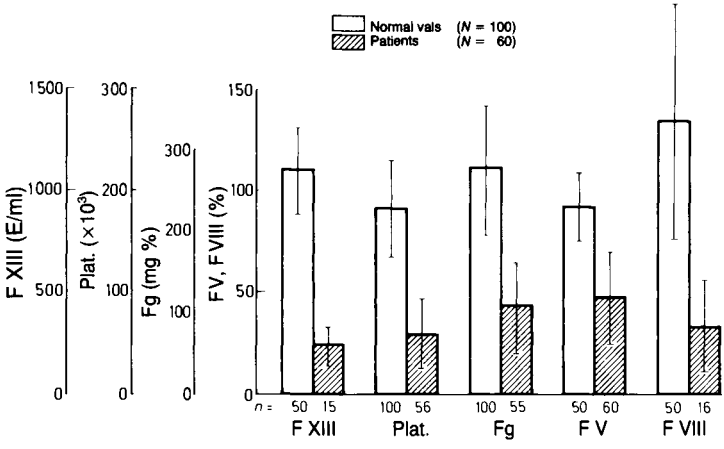


Fig. 4. Diagnosis of consumption coagulopathy: mean difference of individual coagulation analysis factors in 100 normal subjects and a total of 60 patients with consumption coagulopathy (Lasch, 1969)

intravascular coagulation. Serial controls, which allow a tendency to be recognized and confirm the diagnosis, are helpful. Indications about a consumption coagulopathy with and without increased secondary fibrinolysis are provided by the underlying disease, the impairment of organ functions and a state of shock, and also by the type and time of occurrence of a hemorrhagic diathesis. It is often not possible, without costly test combinations, to determine precisely the extent of the synthesis disorder (e.g. hepatic cirrhosis), of the disseminated intravascular coagulation and of the secondary fibrinolysis in a case of hemorrhagic diathesis, since numerous laboratory parameters may prove to be equally pathological in all three cases. A differentiation is important, since it determines the approach to treatment.
Accordingly the following have to be clarified by means of coagulation analysis:

1. A hypercoagulability,
2. A compensated or decompensated consumption coagulopathy,
3. A secondary fibrinolysis,
4. A concomitant disorder of synthesis and
5. A combination of 2, 3 and 4.

A single test does not provide much information. Only a combination of tests makes it possible to classify and assess the degree of severity of the disorder of hemostasis.
A hypercoagulability can be recognized from the shortened coagulation time, the shortened r-time and k-time in the thromboelastogram, an increase in the activity of thrombin-sensitive Factors V and VIII and also, in a great number of cases, through a positive ethanol and protamine sulfate test. A high fibrinogen level and a thrombocytosis are further indicators of a hypercoagulability, in the sense of an increased coagulation potential.
Disseminated intravascular coagulopathy is diagnosed on the basis of clinical signs and the analysis of coagulation parameters. The diagnostic criteria include a predisposing primary illness, hemorrhagic tendency of manifest bleeding and microthrombosis (e.g. cutaneous bleeding) in combination with pathological findings relating to the following coagulation parameters: a thrombocyte count of fewer than 100000–150000/µl, less than 100–150 mg% fibrinogen and a Quick value of less than 40% of normal. Additional factors may also be taken into account, including an increase in fibrogenic cleavage products to

more than 10μg/ml, a decrease in factor VIII to less than 50% of normal levels, a decrease in antithrombin III levels to less than 60% of normal and a positive ethanol gelation test. Progressive changes in these coagulation parameters corroborate the diagnosis.

As mentioned, in *consumption coagulopathy* there is a fall in the thrombocytes and in the coagulation Factors I (fibrinogen), II, V, VIII, X and XIII. The bleeding time and coagulation time are correspondingly prolonged. A thrombocytopenia develops in particular in septic conditions. Fibrinogen/fibrin split products induce a disorder of thrombocyte function. A decrease in the activity of the thrombin-sensitive Factors V and VIII preferentially occurs. It is possible to make a differentiation from a disorder of synthesis through the fact that in the latter case the Factor VIII activity remains in the normal range. In correspondence with the fall in the factors, the thromboplastin time (Quick) and the partial thromboplastin time (PTT) show pathological values. The thrombin time and the reptilase time are normal; prolonged times first occur at fibrinogen concentrations of under 50 mg%. The ethanol test and the protamine sulfate test are considered to be indicators for circulating fibrin/monomer complexes. The ethanol test is of only limited usefulness since at low fibrinogen concentrations of under 40–50 mg% it may yield false negative results despite the presence of monomers, and at fibrinogen concentrations over 400–500 mg% may give false positive even when soluble fibrin is not present in the plasma. More costly procedures for the demonstration of soluble fibrin in the plasma are possible by means of gel filtration, affinity chromatography and N-terminal glycine determination on isolated and precipitated fibrinogen-related material. The fall in the antithrombin III is an important parameter. The fibrinopeptides A and B can be determined by radioimmunology.

In a *fibrinolysis,* as in a consumption reaction a reduction is found in the Factors I (fibrinogen), II, V and VIII. The bleeding time and coagulation time are correspondingly prolonged on the thromboelastogram, and as in consumption coagulopathy a prolongation of the r-time and k-time is found. A disorder of thrombocyte function is present due to the fibrinogen/fibrin split products; when fibronolysis predominates, the thrombocytopenia is less marked, there is not such a marked fall in the antithrombin III level. In correspondence with the reduction in the factors and the inhibitory influence of the split products on the fibrin polymerization, the thromboplastin time (Quick

value), the PTT, thrombin time and the reptilase time are prolonged. By means of chromogenic substrates or immunological procedures, a reduction in the plasminogen and in alpha$_2$-antiplasmin can be demonstrated, and a rise in the plasmin-alpha$_2$-antiplasmin complex can be shown by means of radioimmunology. The fibrinogen/fibrin split products in the serum can be measured semiquantitatively by means of the staphylococcal clumping test, hemagglutination inhibition test and the latex test. Fragment X is still coagulable and is therefore not picked up in the serum. More costly radioimmunological tests make possible the quantitative demonstration of early lytic split products. A peptide, which can be quantified as FCB_3, is released from the C-terminal end of the A-alpha chain. The amino acids 1 to 21 and 1 to 42 are similarly released from the N-terminal end of the B-beta chain at the start of the fibrinogen degradation and can be quantified by radioimmunology. If the fibrinopeptide B cleavage with the amino acids 1–14 from the N-terminal end of the B beta chain has first taken place, these last-mentioned plasmin split products lose their immune reactivity in the test system.

Treatment

The treatment of the disorder of turnover and its consequences is carried out at several levels aimed at the following:

1. Elimination of the cause of the hypercoagulability and of the increased turnover
2. Interruption of the increased turnover
3. Restoration of an adequate hemostatic potential
4. Prevention of microthrombosis and of a disorder of the microcirculation
5. Elimination of the microthrombi and of the microcirculatory disorder (Table 11, Fig. 5).

Disseminated intravascular coagulation is always the consequence of a primary disease. The process is arrested through the elimination of the procoagulatory stimulation: antibiotic therapy in sepsis, cytostatic therapy for leukosis, surgical and cytostatic therapy of isolated tumors, the treatment of shock, removal of the child in the dead fetus syndrome and in some cases of the uterus in infected abortion.

Table 11. Possible therapeutic measures in hemorrhagic complications due to a an increased turnover of coagulation factors and also in hemophilia and coumarin overdosage

Hemorrhagic complications Treatment	Hemophilia	Thrombopenia	Massive transfus.	Consumption & F-lysis	Liver necrosis & LCI	Defibr. Syndr.	Coumarin	Streptokinase
Thrombocyte concentrate		●	●	⊕	●			
Fresh plasma	⊕		●	●	●	●		
AT III			⊕	⊕	⊕	⊕		
Cohn I	⊕		●			●		
PPSB	● (B)				⊕		●	
Heparin			⊕	●	⊕	●		
Vitamin K					⊕*		●	
EACA, aprotinin						●		●
F. VIII conc.	● (A)							
FEIBA	● INHIB							

⊕ Indication dependent on coagulation analysis
* Possible intermittent substitution

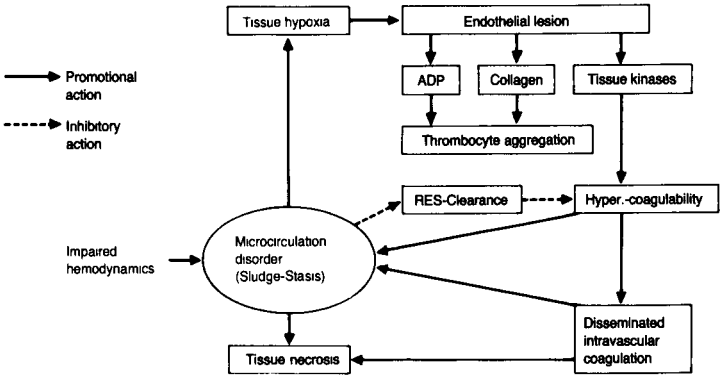


Fig. 5. Perpetuation of the microcirculation disorder in shock (Heene, 1975a, 1977)

Depending on the acuity of the disseminated intravascular coagulation (acute or chronic) and the extent of the secondary increase in fibrinolysis, measures which intervene directly in the hemostasis system, listed under Points 2–5, are necessary. To interrupt the consumption reaction heparin is given intravenously in a dose of 150 to 500 I.U./kg bodyweight in 24 h or 15000–30000 I.U./24 h. Heparin should not be administered subcutaneously, especially in circulatory shock, because of the uncertain situation as regards absorption. Heparin is particularly valuable for prophylaxis, in the initial stage of a consumption reaction when the hemostasis potential is still largely intact and in chronic disseminated intravascular coagulation. In cases of an advanced consumption reaction there is an increased danger of an uncontrollable hemorrhagic diathesis. The action of heparin is dependent on the amount of antithrombin III available in the body. Antithrombin III substitution increases the effect of the heparin. This makes it possible to reduce the dose of heparin. A secondary increase in fibrinolysis regresses without further measures if the activated coagulation is interrupted through heparin therapy.

The success of therapy is monitored on the basis of the elimination of the hemorrhagic tendency, the rise in the fibrinogen concentration, the thrombocyte count and the normalization of the other parameters of coagulation. Pharmacological interruption of the secondary fib-

rinolysis should be avoided as far as possible, since this represents a desirable compensatory mechanism against the development of disseminated intravasal microthrombosis. Only when hyperfibrinogenolysis predominates is the administration of 50000 to 100000 KIU of aprotinin/hour to be recommended. Epsilon-aminocaproic acid and analogous substances are generally contraindicated and should only be used in cases of primary hyperfibrinogenolysis.

In cases of disseminated intravascular coagulation which take an acute course, in which the hemostasis potential has largely been exhausted and there is a general tendency to bleeding, it is advisable to give fresh blood, fresh plasma and fresh frozen plasma. These preparations contain the coagulation factors in inactive form. Activation preferentially takes place at the site of the hemorrhage. In addition inhibitors of coagulation and of fibrinolysis are supplied. As a result of the preparation process factor concentrates often contain small amounts of activated factors which may provoke a disseminated increase in turnover. In cases where the hemostasis potential has been completely exhausted and the capacity of the body for volume loading is impaired, the administration of PPSP, Cohn's fraction, fibrinogen and/or cryoprecipitate may be indicated, but only under the simultaneous administration of heparin. Thrombocyte concentrates may be necessary in leukoses and in sepsis with marked thrombocytopenia. The development of microthrombosis causes an organ-related and a systemic microcirculatory disorder, just as conversely a microcirculatory disorder can result in the deposition of fibrin. In the therapeutic measures the emphasis is upon maintaining adequate cardiovascular function and adequate rheological conditions. In correspondence with the primary disease, attention should be paid to adequate volume substitution through plasma and plasma expanders in hypovolemia; in myocardial insufficiency use must be made of the whole spectrum of drug treatments available. Fibrinolysis therapy with streptokinase or urokinase is indicated in states of progressive shock and persisting microcirculatory disorders due to assumed microthrombosis of the peripheral vascular region of vital organs. This was inaugurated as a concept of therapy by Lasch et al. (1961, 1963). In cases where the hemostasis potential has already largely been exhausted, therapeutic fibrinolysis is associated with a very high risk of bleeding. In well documented individual cases it has been shown however, that recompensation of the circulation can be achieved through the elimina-

tion of the microclots leading to the restoration of perfusion in the peripheral vascular region and through an improvement in the rheological conditions by the degradation of circulating fibrinogen/fibrin monomer complexes which latter increase the viscosity. The dosage amounts to 50–100000 I.U./h. The fibrinolysis treatment is carried out for a period of a few hours.
In chronic consumption coagulopathy without hemorrhagic diathesis, without progressive exhaustion of the hemostasis potential and without the development of microthrombosis, anticoagulation with coumarin derivatives may be successful. The emphasis is upon treatment of the primary disease.

Primary Fibrino-/Fibrinogenolysis

During fibrinolysis therapy with streptokinase, and to a lesser extent with urokinase, a hyperplasminemia develops, especially in the initial phase, with a marked coagulation defect and the development of a coagulopathy. There is a decrease in the fibrinogen, prothrombin, Factor V and Factor VIII; fibrinogen split products show an excessive increase. The disorder of hemostasis regresses relatively rapidly after the discontinuation of therapy. If there is a serious tendency of bleeding, aprotinin (Trasylol), epsilon-aminocaproic acid and their analogues are indicated here. Primary fibrinogenolysis or else very predominant fibrino-/fibrinogenolysis with only slight, almost negligible activation of the coagulation system, may occur in severe liver diseases, prostatic carcinoma, heatstroke, amniotic fluid embolism and also in extensive endothelial cell damage. The differentiation from intravasal coagulation may be difficult, since the same clotting factors are degraded. Clues are provided here by the underlying disease, the usually normal thrombocyte count, the excessive increase in split products, the distinct shortening of the euglobulin clot lysis time and the negative result of the paracoagulation tests (ethanol test, protamine sulfate test). The latter are unreliable indicators, since they can also prove negative when the hemostasis potential has largely been exhausted in consequence of a disseminated intravascular coagulation with and without secondary fibrinolysis.
Some families with a congenital deficiency of alpha$_2$-antiplasmin have been described. A hemorrhagic diathesis with an increased tendency

to bleeding after injuries and surgery is present. Measured using functional methods the alpha$_2$-antiplasmin activity in the plasma lay between 3% and 10% of the norm. The spontaneous clot dissolution and the euglobulin clot lysis time are shortened. No signs of increased fibrinolysis are found in the uncoagulated blood, i.e. no fibrinogen split products can be demonstrated. The increased tendency to bleeding can be normalized with 3 to 4.5 g of tranexamic acid (Ugurol) per day.

Selected Conditions in Which There Is Increased Turnover

Circulatory Shock

Several forms of circulatory shock can be distinguished in correspondence with the primary site of action of the cause of the shock. Cardiogenic, hypovolemic and vagovasally induced shock originate in the macrocirculation. At the start there is a reduction in the cardiac output to below a critical value which leads to reduced perfusion of the peripheral vascular region with the induction of a shock syndrome. Septic shock originates in the microcirculation with the opening up of anatomical and functional arteriovenous shunts resulting in inadequate perfusion of the nutritive capillaries. The supply of blood to the organs, including the heart, is further reduced through an initial activation of intravasal coagulation processes with the possible occlusion of the capillary system through microclots, this aggravating the shock. Following an initial hyperdynamic phase with an increased cardiac output, in the further course of events the septic shock leads to a hypodynamic phase with a reduced cardiac output. In traumatic shock, as a rule several trigger mechanisms such as volume deficiency, trauma reaction and sepsis interact with each other. The genesis and course of the shock is modified according to the various combinations in question.

The microcirculatory disorder induced by the shock leads to tissue hypoxia and acidosis (Fig. 5). As a result the coagulation system can be stimulated in various ways which have a pro coagulatory effect. These stimuli include:

1. Local activation in the peripheral vascular region as a result of hypocirculation, stasis and acidosis with the delayed clearance of activated coagulation products.
2. Hypoxic endothelial damage with the exposure of contact-activating surfaces and subendothelial tissue.
3. The inflow of thromboplastic activities from hypoxic and traumatically damaged tissues.
4. Hemolysis.

Activation of the coagulation system perpetuates the shock-specific microcirculatory disorder through an increase in viscosity in consequence of circulating, soluble, high molecular weight fibrinogen-fibrin monomer complexes and through the development of microthrombi. If the state of shock persists together with the procoagulatory stimulation with excessive demands being made on the inhibitor system, the hypercoagulability of the blood can lead to the exhaustion of the hemostasis potential resulting in hemorrhagic diathesis and possible fibrination of the peripheral vascular region (Fig. 6).
At the same time macrothromboses can occur in the large veins with the complication of pulmonary embolism. If as a result of the disseminated intravascular coagulation and fibrinolysis the hemostasis potential falls below a critical limit, then a hemorrhagic diathesis develops which can aggravate the state of shock through a hypovolemia. A consumption coagulopathy can thus be both the consequence and also the cause of circulatory shock.
Depending on the type of shock, disorders of hemostasis are involved to a varying extent in the shock process. In septic shock fibrin mono-

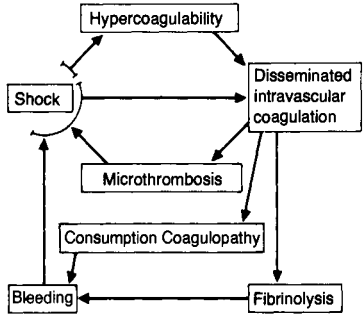


Fig. 6. Interactions between circulatory shock and disorder of hemostasis (Matthias, Lasch, 1981)

mer complexes can be demonstrated in the plasma in almost all cases, and in cardiogenic and traumatic shock in about ¾ of the patients; in hemorrhagic shock and the other forms of shock the proportion of fibrin monomer complexes which can be demonstrated on coagulation analysis is less. Secondary fibrinolysis is rather rarely found in cardiogenic and septic shock whereas in traumatic and hemorrhagic shock and also in the other forms of shock it is seen more frequently. Massive transfusions of whole blood in hemorrhagic and traumatic shock can aggravate the coagulation disorder. Whole blood which has been stored for some time no longer contains any material with a hemostatic action. Procoagulatory substances and fibrinolytic degradation products accumulate on the other hand. In addition a dilution coagulopathy is induced. The forms of shock with the highest mortality demonstrate the highest frequency of coagulation activation, documented by the demonstration of soluble fibrin in the plasma; in these cases the amount of fibrinolysis tends to be rather slight.
The treatment of the hemostasis disorder induced by the shock consists primarily of the elimination or treatment of the cause of the shock. The improvement in the microcirculatory disorder which this produces often leads to the spontaneous regression of the hemostatic disorder. Volume losses and extensive exhaustion of the hemostasis potential should preferably be treated with fresh blood, fresh plasma and fresh frozen plasma. Heparin therapy is indicated in septic and cardiogenic shock.
The use of anticoagulants is restricted in hemorrhagic and traumatic shock because of the organ and tissue injuries. In hemorrhagic shock where increased turnover can often not be demonstrated or only to a slight extent, there is no need for heparin therapy.

Sepsis

The disorder of hemostasis in sepsis is complex in nature. 60% to 70% of the patients have a coagulation defect. In about 35% no deviation from the norm is seen for the coagulation analysis parameters. In normotensive sepsis a classic disseminated intravascular coagulation (DIC) only occurs in just over 10% of the patients. One third of these patients bleed. In septic shock the percentage of patients with DIC increases up to 80% depending on the patient material. On the other

hand a DIC is the consequence of sepsis or septic shock in about 60%. The possibility of the degradation of clotting factors taking place through non specific proteolysis (elastase from leukocytes) which is superimposed upon or even occurs independently of a disseminated intravascular coagulation process, must also be included in the deliberations in sepsis.

A fall in the vitamin-K-dependent clotting factors without any other signs of a DIC is found in 25% to 30% as a consequence of a disorder of synthesis in liver damage which is due to sepsis.

A thrombocytopenia is demonstrated in ca. 55% (sometimes in 100%) of the patients. An isolated thrombocytopenia is found in somewhat less than 40% of cases. The consumptive thrombocytopenia (with and without DIC) is the dominant coagulation defect in sepsis. It can be caused by:

1. the action of thrombin in the context of a DIC
2. direct bacterial endotoxic damage to the thrombocytes
3. an immune-mediated destruction of thrombocytes and
4. the aggregation of thrombocytes on vessel walls with bacterial endotoxic damage (Fig. 7).

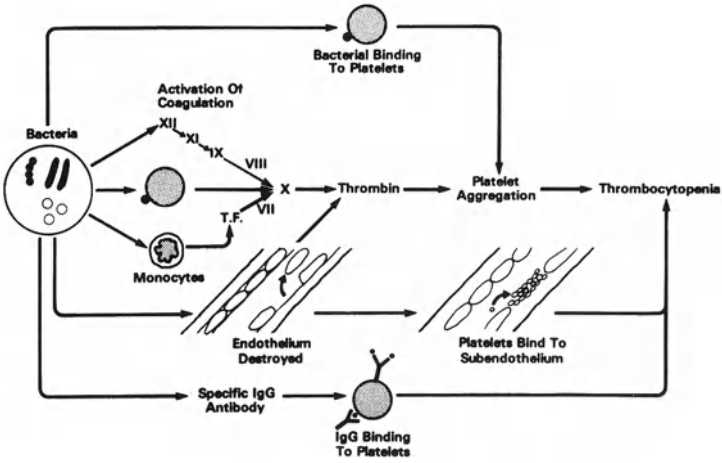


Fig. 7. A schematic summary of various pathways whereby bacteria could induce thrombocytopenia (modified from Wilson et al. 1982)

In normotensive sepsis and thrombocytopenia alone or a reduction in the prothrombin complex factors without the criteria of a DIC, heparin in a low dosage (ca. 10000 I. U./day) and/or the administration of fresh plasma is indicated. In septic shock, manifest DIC and progressive exhaustion of the hemostasis potential, heparin is the drug of choice (20000 to 30000 I. U./day). Antithrombin III substitution is very important. Fresh plasma and possibly factor concentrates supplement the therapeutic concept. If bleeding is present heparin in a reduced dose is justified or should be avoided altogether in favor of antithrombin III and fresh plasma.

Shock Lung

This syndrome will be discussed here only to the extent that coagulation processes are involved in its development (Figs. 8 and 9). Shock lung, or the **a**cute **r**espiratory **d**istress **s**yndrome of adults (ARDS) occurs in about 5% of patients with shock. The syndrome is not necessarily always associated with the presence of a manifest state of shock. Predisposing factors are extensive trauma to the tissues, infections, sepsis, heavy blood losses, intoxications and lung damage due to irritant gases. It is always accompanied by a generalized or local activation of the plasmatic coagulation system and of the thrombocytes, which need not always be demonstrable on coagulation analysis, but which can also lead into a consumption coagulopathy. As regards the pathophysiology it is initially characterized by vaso- and bronchoconstriction with a change in the ventilation/perfusion ratio. In the further course of the condition a hypoxic and humorally induced barrier disorder of the alveolocapillary membrane structures develops, initially with interstitial, later with alveolar protein- and fibrin-rich exudate and a progressive diffusion disorder (exudative alveolitis).
The late phase is characterized by connective tissue proliferation (sclerosing alveolitis) with progressive hypoxemia and hypercapnia. Even in the early phase of shock, long before the development of a respiratory insufficiency, pathomorphological changes can be demonstrated in the lungs. Depending on the type of shock, thrombocyte and granulocyte aggregates are found to a varying extent and also fibrin thrombi in the arterioles and capillaries, but also in the venules. The

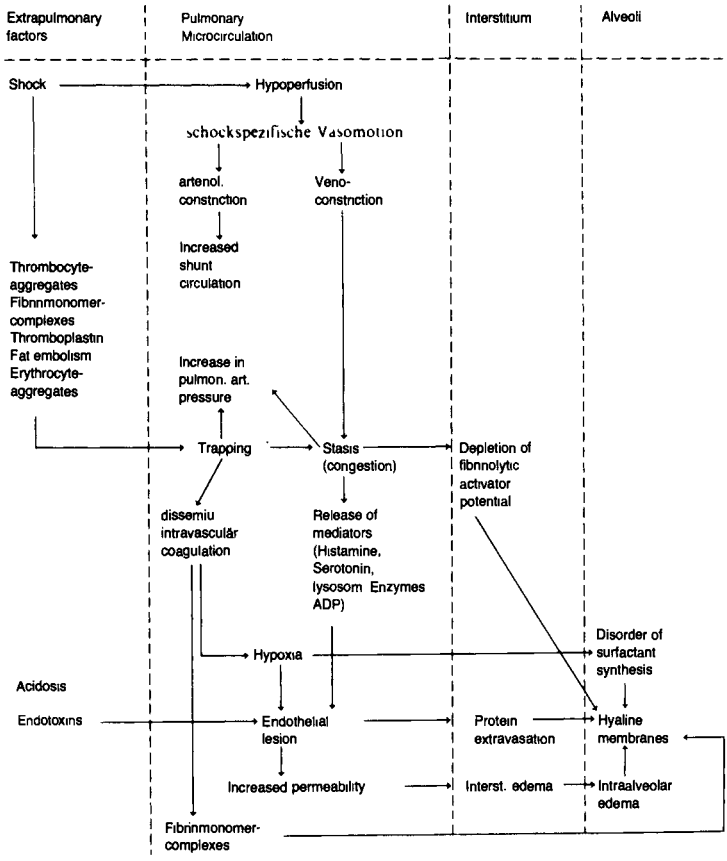


Fig. 8. Pathogenetic factors in the development of shock lung (Heene, Lasch, 1977)

fibrin is seen on histology as microclots and as hyaline globules (shock bodies). The clots and aggregates have only partly originated in the pulmonary circulation itself, they are mostly carried to the lungs as emboli from the venules of the systemic circulation in generalized activation of coagulation. The lungs already normally act as a filter organ for activated coagulation products. In the initial phase a so-

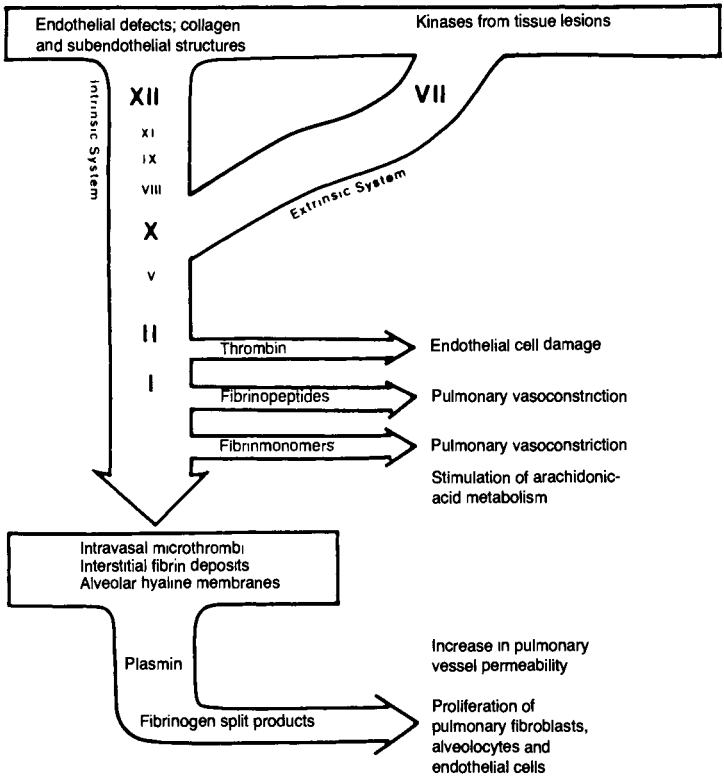


Fig. 9. Significance of the involvement of coagulation and fibrinolysis products in the pathogenesis of so-called shock lung (Neuhof et al., 1982)

called early microembolism syndrome occurs, in which thrombocytes, fibrinopeptide B and early degradation products of the fibrin – a pentapeptide has been identified – are said to be involved in functional changes of the lung in the form of a vasoconstriction and bronchoconstriction. The thrombocytes release vasoactive substances with serotonin and histamine. The thromboxane A_2 which is formed by the thrombocytic prostaglandin system is a potent vasoconstrictor. The complement activation leads by chemotaxis to intrapulmonary

granulocyte adhesion with the release of lysosomal enzymes and activation of the granulocytic prostaglandin system with the formation of vasoactive cyclooxygenase products and membrane-damaging leukotrienes via the lipooxygenase pathway. The pulmonary vessel endothelium is initially still intact and plasminogen activator, prostacyclin which has a vasdilatory action, but also prostaglandin $F_{2\alpha}$ with a vasoconstrictive action, are released from the capillaries. The kininase 2 which is still available converts angiotensin I into the vasoconstrictive angiotensin II. Whereas the fibrin thrombi and cell aggregates are initially still reversible, the fibrination increases in the further course of the condition. In this so-called late microembolism syndrome fibrin elimination is delayed. A fibrinolysis inhibitor can be demonstrated in the systemic blood. The vessel permeability is increased through the local release of fibrinolysis products, complement, histamine, endotoxin and leukotrienes. The increasing damage to the vascular endothelium of the pulmonary circulation leads to an impairment of the formation and release of prostacyclin, plasminogen activator and kininase 2. The development of edema predominates. As mentioned, fibroblast proliferation subsequently occurs, which is also provoked by fibrin degradation products.
Treatment aimed specifically at the coagulation system has little influence on the prevention and treatment of the shock lung syndrome. Heparin may be of some value for prophylaxis, but progression of the changes will presumably not be prevented. Fibrinolytic treatment does not seem to be indicated. It is not certain whether prostacyclin infusions are of value in the initial phase.

Gynecological Diseases

In about 30% to 40% of patients with *premature abruptio placenta* a disorder of coagulation occurs with a fall in the fibrinogen, the thrombocytes, and a rise in the split products. The inflow of thromboplastic material of the placenta from the uterus into the maternal circulation and a local consumption of coagulation factors in the retroplacental hematoma are said to be causally responsible. If the mother loses a lot of blood the consumption coagulopathy is additionally induced and maintained by the circulatory shock. The possibility has also been discussed that a disseminated intravascular coagulation

with secondary fibrinolysis represents the primary pathological process, which through hemorrhages, thrombi and necroses in the region of the insertion of the placenta leads to the detachment of the placenta, which then perpetuates the coagulation disorder. The coagulation-specific therapy consists of the administration of fresh blood, fresh plasma, fresh frozen plasma, fibrinogen and possibly Cohn's fraction I and also cryoprecipitate. Consumptive coagulopathies with fibrinolysis showed successful recompensation under the additional administration of aprotinin (Trasylol). Heparin is not indicated because of the uterine bleeding. Hyperfibrinolyses can be inhibited with aprotinin. In rare cases epsilon-aminocaproic acid and its analogues are indicated.
Amniotic fluid which has a thromboplastic action and which has been swept into the maternal circulation seems to be the cause of the coagulopathy in *amniotic fluid embolism.* Cells, cell detritus, and tissue constituents from the amniotic fluid and also platelet-fibrin thrombi are mainly found in the pulmonary circulation. The obstruction of the vessels and in particular the concomitant vasoconstriction can lead to an acute cor pulmonale with circulatory insufficiency, and this can maintain the coagulation disorder. In the further course of the condition a shock lung syndrome develops. Besides the disseminated intravascular coagulation the secondary fibrinolysis is very predominant. Heparin is indicated in the initial phase. If the hemostasis potential is exhausted, fresh blood, fresh plasma, fresh frozen plasma, fibrinogen, Cohn's fraction I, cryoprecipitate and if fibrinolysis predominates, aprotinin are necessary.
The coagulation disorder following *intrauterine death of the fetus* ("dead fetus" syndrome) is predominantly a consumption coagulopathy. With the exception of rare cases, a secondary fibrinolysis is rather less marked. The disorder of coagulation develops in about the 3rd week after the death of the infant. The cause of the hemostasis disorder is not clear; the absorption of proteolytic enzymes from the dead fetus into the maternal circulation is assumed. The increased turnover often takes a chronic course. Treatment of the coagulation disorder has been described in the preceding section.
In *septic abortion* the coagulation disorder is a consequence of the endotoxinemia. One is mostly dealing with gram-negative organisms *(Escherichia coli).* The disorder of hemostasis corresponds to that seen in sepsis and septic shock due to other causes. The pregnancy with the increasing hypercoagulability in the last trimester, is to be seen as a

predisposing factor for the consumption coagulopathy. A secondary fibrinolysis is less important. There is mostly marked thrombopenia. Heparin can be considered for therapy but the results are rather uncertain. Substitution therapy is carried out in accordance with the guidelines given. The course of a chorioamnionitis basically corresponds to that of sepsis and septic shock.

Hypercoagulability and disseminated intravascular coagulation processes are similarly seen in *preeclampsia and eclampsia.* The fibrinolytic activity tends to be rather reduced, and secondary fibrinolysis rarely occurs in this coagulopathy. The disseminated intravascular coagulation mostly takes a latent course. Acute consumption reactions are rare. Fibrin depositions are found in the microcirculation, especially in the kidneys. Fragmented erythrocytes are interpreted as the consequence of a microangiopathically induced hemolysis. Heparin therapy is not indicated in patients with the full-blown picture of eclampsia.

Transitional states are found between this and the *hemolytic-uremic syndrome* during pregnancy and the post-partum phase. Here thrombocytopenia, hemolytic anemia with fragmented cells and renal failure predominate. The syndrome may first occur several weeks after the birth.

Liver Diseases

Manifest consumption coagulopathies first occur in hepatic diseases in the advanced stages of a hepatic cirrhosis and in acute hepatic dystrophy. The pathological mechanism has been described elsewhere. The coagulation disorder is a complex one. As a rule this consists of a combination of a disorder of synthesis of the coagulation factors which are formed in the liver, a latent, chronic, but in phases also acute increase in turnover of the coagulation factors and of the thrombocytes with and without fibrinolysis and also a thrombocytopenia due to sequestration in the spleen.

Disorders of Hemostasis in Liver Diseases

Significance of the Liver for Hemostasis

The liver has to fulfil several functions within the coagulation system (Fig. 2):

1. It is responsible for the synthesis of the majority of the plasmatic coagulation and fibrinolysis factors (cf. Chapter I);
2. It is the production site for numerous inhibitors of the coagulation and fibrinolysis system;
3. The reticuloendothelial system of the liver is primarily involved in the elimination of activated and inactivated coagulation and fibrinolysis factors and their degradation products.

The clotting factors of the prothrombin complex (Factors II, VII, IX, X) and fibrinogen are synthesized in the liver. The site of synthesis of the clotting Factors V, VIII and XIII is still not clear to some extent. Factor V also seems to be formed in the liver. Factor VIII consists of two subunits. The formation of the Factor VIII-associated antigen is localized in the liver, whereas that part of the Factor VIII molecule complex which is responsible for the procoagulatory activity is presumably formed ubiquitously in the endothelium. Factor XIII similarly consists of two components. The a-chain which is responsible for the Factor XIII activity is probably formed outside of the liver, whereas the site of synthesis for the b-chain is the liver. The liver is also the production site for plasminogen and the inhibitors alpha$_2$-antiplasmin, alpha$_2$-macroglobulin and alpha$_1$-antitrypsin. Plasminogen proactivator is released ubiquitously from endothelial cells. The elimination of altered plasma constituents is a general principle of the reticuloendothelial system. The clearance capacity of the liver is high, since about 50 to 80% of the total reticuloendothelial system, in the form of the Kupffer cells, are concentrated on the liver and the liver requires about 20 to 25% of the cardiac output. The liver takes from the blood activated coagulation factors with a procoagulatory action, activated fibrinolysis factors, and aggregated and degraded factors of the hemostasis system.

Pathophysiology of the Hemostasis Disorder in Liver Diseases

Pathogenetic mechanisms are involved in the genesis of the hemostasis disorder in hepatic diseases:

1. A reduced synthesis of coagulation factors and fibrinolysis factors and also of their inhibitors because of an impaired synthesis performance of the hepatocytes.
2. The impairment of the clearance function of the reticuloendothelial system of the liver leading to an accumulation of activated coagulation and fibrinolysis products within the systemic circulation.
3. The circulatory disorders in portal hypertension with reduced hepatic perfusion and shunt circulation.
4. The loss of factors of the hemostasis system in the enlarged extravasal space.
5. The sequestration of thrombocytes in the spleen with splenomegaly.

These five components of a hemostasis disorder may be of varying importance in the course of the different diseases of the liver, thus influencing the clinical picture and the therapeutic deliberations.

The hepatogenic disorder of hemostasis occurs in the form of a disorder of synthesis and of turnover. In dependence on the impaired synthesis performance of the hepatocytes and the reduced availability and utilization of vitamin K, there is a decrease in the activity of the prothrombin complex.

It has been demonstrated by immunological methods that although the prothrombin antigen falls in the course of hepatic diseases, it is present in a larger amount than would be expected from the activity measured using functional methods, so that it can be assumed that a defective, incomplete prothrombin molecule is formed, which corresponds to the so-called PIVKA (*p*rotein *i*nduced by *v*itamin *K a*bsence or *a*ntagonist). From this is deduced the rationale for the therapeutic parenteral administration of vitamin K in severe damage of the hepatic parenchyma, in which obstructive bile duct disease does not play any part.

The fibrinogen level does not fall until there is progressive destruction of the hepatic tissue and may be raised in inflammatory liver diseases as acute phase protein, but also in portal hypertension because of an increase in the rate of synthesis. A fall in the fibrinogen is always a sign of severe liver disease. In addition defects can occur in the molecular

structure of coagulation factors formed during liver diseases, e.g. in the form of a dysfibrinogenemia.
The disordered turnover also has the effect of producing continuous activation of the coagulation system with or without an increase in fibrinolysis. It is often difficult to estimate the importance of this hemostasis disorder, to be classified as a consumption coagulopathy with or without an increase in fibrinolysis, in the course of liver diseases. The procoagulatory stimulation which takes place intravasally initially leads to a hypercoagulability. The absence of inhibitor potential of the coagulation – antithrombin III – can set in motion a disseminated intravasal coagulation process, which may involve the thrombocytes and lead to the development of local micro-thrombosis (preferentially in the liver also), to the disseminated deposition of fibrin in the entire peripheral vascular region and to macrothromboses. In correspondence with this increased activity of the thrombin-sensitive factors (Factors V, VIII, XIII) is initially found, which in the further course of the condition together with other factors turns into a reduction in activities.
Plasminogen coprecipitated with the fibrin thrombi is converted by endothelial activator into plasmin and in the form of a secondary increase in fibrinolysis leads to the dissolution of the thrombi. Thus both activators of fibrinolysis and also fibrin split products are swept into the systemic circulation. With a simultaneous reduction in the inhibitor potential a systemic activation of the fibrinolysis system commences. This results in the degradation of fibrinogen with the formation of fibrinogen split products and a further impairment of the hemostasis system. In the extreme case total defibrination may occur with a marked tendency to bleeding. In correspondence with the course of the disease the turnover disorder may take an acute or chronic course. The impaired clearance function of the reticuloendothelial system and the disorders of the portal circulation are said to be responsible for perpetuating the turnover disorders, especially in chronic consumption coagulopathy in the course of a hepatic cirrhosis with portal hypertension.

Clinical and Coagulation Analysis Aspects of Hepatogenic Hemorrhagic Diathesis

About 15% of patients with hepatic cirrhosis bleed as a result of hemorrhagic diathesis. Excluded are patients with bleeding from esophageal varices and hemorrhages from other identifiable bleeding sources. The hemorrhagic diathesis manifests itself in mucosal bleeding, epistaxis, and bleeding from the gingiva and skin. The latter occurs when the plasmatic coagulation system is primarily involved, in the form of bruises, suffusions and hematomas; more petechial-type bleeding points to a thrombocytopenia. One or more pathological coagulation tests are found in 85% of patients with hepatic cirrhosis (Fig. 10).

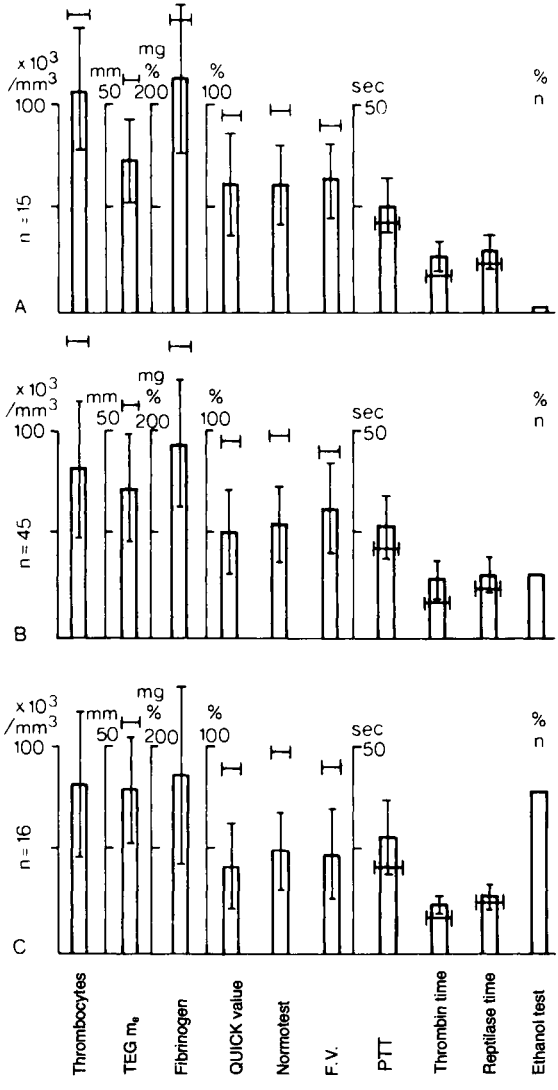
On coagulation analysis it is a question of differentiating between:

1. A reduced synthesis of the coagulation factors
2. An increased consumption of coagulation factors
3. A change in the inhibitor potential
4. The occurrence of functionally defective coagulation factors
5. A thrombocytopenia and a thrombocytopathy.

Because of the many different pathological mechanisms responsible for the hepatogenic disorder of hemostasis, the interpretation of pathological changes in coagulation analysis parameters may be difficult and it may prove impossible to classify the hemostatic disorder in respect of whether it is a disorder of formation or turnover.

Disorders of Hemostasis in Various Liver Diseases

In *obstruction of the draining bile ducts* (cholelithiasis, tumor compression, biliary cirrhosis etc.) the absorption of lipid soluble vitamin K is reduced. A reduction in vitamin K absorption also occurs in malabsorption syndrome (plancreatic insufficiency, inflammatory diseases of the small intestines). After about 10 to 14 days the vitamin K depots have been exhausted. The Quick value falls by 40 to 50%. The intravenous injection of 1 to 5 mg of vitamin K causes the Quick value to rise to the normal range within 24 h and, with some reservations, can provide information about hepatocellular damage (Koller test). As a rule a manifest hemorrhagic diathesis does not occur.



TEG m_e = e thromboelastogram, max. amplitude;
F.V. = Factor V;
PTT = partial thromboplastin time;
I—I = normal values; 100 controls

Fig. 10

The disorder of hemostasis in *hepatocellular diseases* is characterized by a disorder of synthesis and an optional disorder of turnover. The extent and proportionate distribution of the coagulation disorders depend on the nature, the extent and the course of the liver cell disease.

Because the disorder of hemostasis is often a complex one, it is not possible to draw conclusions about the extent and prognosis of the hepatic disease on the basis of just one coagulation analysis. Quite good information about the development of the disease picture can be obtained from short-term serial controls however.

In *acute hepatitis* (hepatitis A, hepatitis B, non-A, non-B hepatitis) a decrease in the activity of the prothrombin complex factors is a sign of a disorder of vitamin K utilization in the postribosomal phase of prothrombin formation with a simultaneous more or less marked impairment of the protein synthesis performance of the hepatocytes. In correspondence with the half-life, Factor VII falls first, followed by Factors II, X and IX.

With Quick values above 50% the Normotest shows a good correlation with the impairment of synthesis performance of the prothrombin complex and is informative in the initial stage of the impaired liver function. In advanced liver disease and where there are low prothrombin levels, the Thrombotest provides more reliable information about the synthesis performance of the liver cells. During the regression of a hepatitis the Hepato-Quick and the Normotest show a tendency to normalization earlier than the transaminases. With reservations this makes it possible to draw conclusions about the prognosis. The immunological determination of the prothrombin often results – as in other liver diseases – in higher values than the activity measurement, so that the vitamin-K-dependent postribosomal completion of the prothrombin molecule can be more greatly disordered than the protein synthesis. With a Quick value below 30% the disease can be

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Fig. 10. Coagulation analysis findings in patients with chronic liver diseases. A: chronic hepatitis (n = 15); B: hepatic cirrhosis and portal hypertension (n = 45); C: hepatic cirrhosis, portal hypertension and bleeding from esophageal varices (n = 16). (Heene, 1974b, 1975c). TEG m_e = thromboelastogram, max. amplitude; F.V. = Factor V; PTT = partial thromboplastin time; I = normal values; 100 control subjects

expected to take a severe course. The fibrinogen level may be raised because of increased synthesis and first falls in the advanced stage. It is influenced by simultaneously occurring increases in turnover of the coagulation and fibrinolysis. With progression of the liver damage there is a fall in the activities of Factors V and XIII. These can also be influenced by increases in turnover. The Factor VIII activity and the concentration of the Factor-VIII-associated protein show a distinct rise. They become normal as the hapatitis resolves. A persisting increase can be interpreted as indicating development into a chronic hepatitis. Antithrombin III, plasminogen and alpha$_2$-antiplasmin are lowered and may promote an increase in turnover. Secondary liver diseases (tuberculosis, sarcoidosis) rarely lead to coagulation changes.
The *form of hepatitis which takes a necrotizing course* and severe toxic liver damage show a marked disorder of synthesis of the prothrombin complex factors and of the other coagulation proteins formed in the liver. If the factors of the prothrombin complex fall below 20% of the norm, a manifest bleeding tendency occurs. At the same time there is often an increase in turnover which can lead to consumption coagulopathy. Intrahepatic microthrombosis occurs, and this persists because of the absence of plasminogen activator in the liver. This leads to further impairment of hepatic function. Fibrin which has not been cleared in the liver and is precipitated in the peripheral vascular region induces the release of plasminogen activator out of the vascular endothelium of the lungs and the rest of the microcirculation, this initiating the secondary fibronolysis. The fibrinolysis and the resulting hemostasis defect are maintained by the reduced RES clearance in the liver for fibrinolysis activators and the fibrinogen-/fibrin split products. A thrombocytopenia and a functional thrombocyte defect promote the disorder of hemostasis.
The collapse of the hemostatic potential is documented through the following coagulation-analysis parameters: thrombocyte count below 50000/mm^3, fibrinogen below 100 mg/100 ml plasma, Quick value below 20%, partial thromboplastin time over 60 s, Factor V below 20%, thrombin and reptilase times over 30 s, ethanol gelation test positive, fibrinogen/fibrin split products in the serum positive.
In *chronic persistant and chronic aggressive hepatitis* only discrete changes are seen in the form of a reduced synthesis performance (Fig. 10). As a rule no manifest disorder of hemostasis is present. The coagulation parameters may deteriorate during an acute attack of

chronic hepatitis and be additionally influenced by a concomitant increase in turnover. A thrombocytopenia of varying extent is present, the Factor VIII activity and Factor VIII antigen are raised.

In *liver cirrhosis* the coagulation analysis parameters are found to be distinctly pathological with a hemostasis defect which in advanced stages leads to a manifest hemorrhagic diathesis (Figs. 10 and 11). The causes of this are a disorder of synthesis as a result of the reduction in functional hepatic tissue and a disorder of turnover through the impairment of the RES clearance function and the progressive development of a bypass circulation. The synthesis of functionally defective fibrinogen leads, via a disorder of fibrin polymerization, to an increase in the hemostasis defect. The fibrin concentration may be

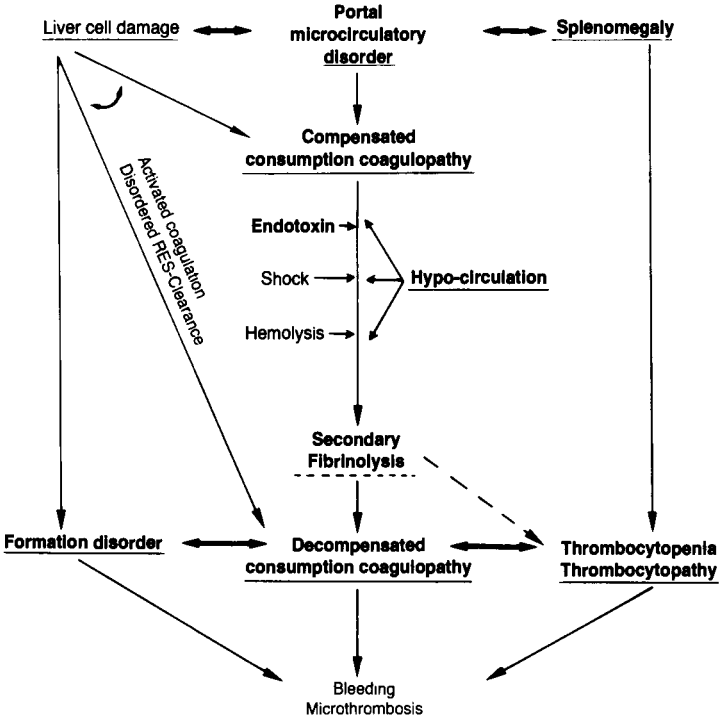

Fig. 11. Pathogenesis of the hemostasis defect in portal hypertension (Lasch, 1976)

raised in consequence of a transient increase in synthesis. A hypofibrinogenemia is due to reduced synthesis, increased diffusion into the extravasal space and to an increase in turnover in the form of a consumption coagulopathy. This is accompanied by a thrombocytopenia, which is increased through sequestration of the platelets in the spleen.

The consumption coagulopathy with a secondary increase in fibrinolysis is promoted through the reduced clearance capacity of the RES in the liver with a simultaneous reduction in the inhibitors antithrombin II and alpha$_2$-antiplasmin. Progression of the hemostatic disorder found in hepatic cirrhosis occurs in esophageal varices hemorrhage as a result of the hypovolemia and hemorrhagic shock. Fibrin monomers can be demonstrated in the circulation (ethanol test, FM test). The microcirculatory disorder induced through shock is a decisive factor for the progression of the increased turnover and consumption coagulopathy. Since as a rule hemorrhage of esophageal varices occurs independently of the degree of the hemostatic disorder, the latter seems to be of subordinate importance for its induction.

In hepatic cirrhosis the hemostatic defect is represented by the following coagulation analysis parameters: thrombocytes below 100000/mm^3, fibrinogen below 200 mg/100 ml plasma, Quick value below 50%, partial thromboplastin time above 50 s, Factor V below 50%, thrombin and reptilase times over 50 s, ethanol gelation test negative (with increased turnover during esophageal varices hemorrhage ethanol test becomes positive), fibrinogen/fibrin split products in the serum positive.

In *portocaval anastomosis* the reduced clearance capacity of the hepatic RES persists. The change in the coagulation analysis parameters is due to the reduced synthesis performance of the liver combined with an increase in turnover, a thrombocytopenia and a secondary fibrinolysis. The disorder of hemostasis remains compensated for as long as the hepatic disease is stationary. In *primary liver tumors* and *extensive hepatic metastases* a raised coagulation potential is found with hyperfibrinogenemia. A hypercoagulability of the blood gives rise to an increased tendency to thrombosis. Coagulation analysis changes are seen in primary hepatic tumors in the form of a consumption coagulopathy. In cases of *liver transplantation* a consumption coagulopathy is found in the anhepatic phase followed by a secondary increase in fibrinolysis, which is due to the transient loss of the hepatic

RES and the trauma of the operation. The coagulation changes become normal after transplantation of the donor liver and revascularization in the course of the next few days. The increased turnover is perpetuated if a hypoxically damaged liver is transplanted or a graft rejection reaction develops. Intrahepatic microthrombosis develops. The thrombocytopenia is due to a consumption reaction and in the further course of the condition to immunological processes.

Treatment of the Hepatogenic Hemostatic Defect

Treatment of the primary disease comes first, and with its improvement the hemostasis also becomes normal. The coagulation-specific therapy is merely symptomatic, so as to bridge over or prevent episodes of hemorrhagic diathesis resulting from impaired synthesis of the coagulation factors, a consumption coagulopathy with and without fibrinolysis and also micro- and macrothrombotic events.
The administration of vitamin K leads at the most to only moderate success in respect of the increase in the activities of the prothrombin complex factors. To a certain extent the impairment of the post-ribosomal conversion of the prothrombin complex precursors can be increased in the active coagulation factors. Taking possible circulatory reactions into account, the administration should be carried out intravenously. 10 mg of vitamin K per week is sufficient. With a higher dosage a further fall in the Quick value has occasionally been found, this being due to the conversion of vitamin K into vitamin K epoxide, which does not possess any functional activity, but which competitively inhibits the action of vitamin K.
If blood transfusions are necessary for hemorrhagic complications, then preference should be given to fresh plasma and erythrocyte concentration (Table 11). Stored blood products contain activated coagulation products and thrombocyte aggregates which have a procoagulatory action and are sequestered in the pulmonary circulation. Stored blood is of no hemostatic value, because in the course of the storage a decrease takes place in the activity of the coagulation factors, especially of the labile Factors V and VIII. The use of factor concentrates to eliminate the hemostatic defect is problematical.
As a result of the preparation process the factor concentrates contain a certain percentage of activated coagulation factors which have a pro-

coagulatory action. Prothrombin complex preparations should only be given if the hemostasis potential has been completely exhausted and for uncontrollable hemorrhage; if it is justified on the basis of the hemorrhagic diathesis they should be given together with small amounts (5000 to 7500 IU/24 h) of heparin. Fibrinogen substitution may be necessary in the context of a defibrination syndrome. Fibrinogen preparations and Cohn's fraction I are available. The latter additionally contains Factors V and VIII. The dose amounts to 2 g to 3 g of fibrinogen per 8 to 12 h. The concomitant administration of heparin is to be recommended. Preference should be given to the administration of fresh plasma or fresh frozen plasma. Compensation of the hemostasis can be achieved with ca. 1 liter of fresh plasma in most cases. Surgical procedures can be carried out once the concentration of the factors has reached 50% of the norm and the fibrinogen lies above 100%. Over-compensation may be accompanied by thromboembolic complications.

The therapeutic action of heparin treatment is doubtful. As a rule an additional defect of hemostasis is created, without any recompensation of the coagulation disorder through an increase in the factors, which is what is desired by interrupting the assumed increase in turnover. Heparin seems to be indicated only if fibrin monomers can be demonstrated in the plasma (ethanol test) and in esophageal varices hemorrhage with a state of shock in which the development of a consumption coagulopathy is to be assumed. The mean dosage lies at 10000 IU to 15000 IU/24 h, corresponding to 150 IU to 200 IU/kg bodyweight and 24 h. Monitoring by means of the thrombin time is of no use, because this is prolonged through the complex disorder of hemostasis with hypofibrinogenemia and fibrin/fibrinogen split product complexes.

Substitution can be performed with antithrombin III concentrates. Through this physiological inhibitor of coagulation and fibrinolysis an increased turnover can be successfully suppressed. The mean dosage amounts to 1000 IU to 2000 IU per day. In some cases heparin therapy is not necessary.

Apart from a few exceptions antifibrinolytic agents are contraindicated. Epsilon-aminocaproic acid and equivalent preparations can increase a consumption reaction with fibrin deposition in the peripheral vascular region. In cases of marked fibrinolysis the use of aprotinin is justified. In contrast to epsilon-aminocaproic acid it

inhibits plasmin directly. The mean dosage amounts to 500000 KIU to 2 million KIU/24 h. Simultaneous heparinization should be considered.

Cardiopulmonary Bypass

During cardiac surgery with extracorporeal circulation a coagulation disorder necessarily occurs during the operation and in the postoperative period. Intraoperatively this is due to the need for heparin anticoagulation. The initial dose of heparin before being connected to the heart/lung machine amounts to 200 to 300 (up to 400) I.U./kg bodyweight. 100 to 150 I.U./kg are given every hour after the start of the bypass. The neutralization of the heparin at the end of the bypass time is carried out with 150 to 200 (up to 300) I.U. protamine chloride (Roche)/kg bodyweight. The ratio of the total dose of heparin to that of protamine chloride should be roughly 1:0.5–0.8. In addition there is a disorder of hemostasis induced by the nature of the surgical procedure, which persists after the operation has been completed and if there are no complications, resolves within 2 to 4 days. Apart from the heparinization, changes in the coagulation system during and after cardiac surgery and extracorporeal circulation are due to the following causes. As a result of the operation trauma thromboplastic substances are released into the circulation. The lungs and pleura in particular are rich in procoagulatory substances and activators of fibrinolysis. An activation of coagulation and fibrinolysis is induced through contact of the blood with the foreign-body surfaces of the bypass-system. Procoagulatory substances are released through the hemolysis of mechanically damaged erythrocytes. The thrombocytes develop functional defects and increased turnover. If there are fairly heavy blood losses, an additional disorder of hemostasis is caused by transfusions. Postoperative circulatory insufficiency or a state of shock leads to increased turnover in the form of a consumption coagulopathy with and without concomitant secondary fibrinolysis. With impaired clearance function of the RES the disseminated microthrombosis aggravates the shock process. A generalized bleeding tendency develops through the exhaustion of the hemostasis potential in the systemic blood. The following changes can be demonstrated in the coagulation system. Neglecting the dilution effect resulting from the filling volume

of the extracorporal circulation the thrombocytes fall to 50 to 70% of their baseline value. The disorder of thrombocyte function becomes apparent in a reduced capacity of the platelets for adhesion and aggregation, which is accompanied by the release of platelet-specific constituent substances. A prolonged bleeding time is the consequence. Even when there are no complications, a fall regularly occurs in the Quick value, the fibrinogen, and the activity of Factors II, V, VIII and X. The Factor VIII antigen is raised. A reduced plasminogen and antithrombin III level is also measured. The activities and concentrations of the clotting factors fall to 50% of the norm. The fibrinogen fibrin split products are regularly raised. The ethanol gelation test is positive in a large number of the patients. The defect of thrombocyte function and increased fibrinolysis are considered to be primarily responsible for the coagulation disorder observed and the hemorrhagic diathesis. The disorder of thrombocyte function is increased through the known or unknown perioperative administration of aggregation inhibitors, analgesics, diuretics and antibiotics. A primary fibrinogenolysis leads to a fall in the fibrinogen and in the activities of Factors V and VIII and might suggest a disseminated intravascular coagulation. A consumption coagulopathy with a progressive fall in the coagulation factors becomes of increasing importance if multiple transfusions are necessary, and if circulatory shock and sepsis are present. Postoperative coagulation defects might additionally be due to the continuing action of heparin with an underdosage of protamine, in the heparin-rebound phenomenon and with an overdosage of protamine. In the latter case arrhythmias, thrombocytopenias and increased fibrin polymerization may occur. These phenomena regress in the early postoperative phase however. A coagulation disorder increases in dependence on the intra- and postoperative blood losses and the length of the bypass time.

Assuming a normal preoperative coagulation status, the perioperative coagulation analysis comprises determinations of the bleeding time, the Quick value, the thrombin time, the reptilase time, the thrombocyte count and the serum concentration of split products.

During the early postoperative phase 80% of the patients show coagulation analysis changes within the first 18 h, which however, do not militate against adequate hemostasis. In 20% of the cases a marked defect of hemostasis is present which can cause a manifest hemorrhagic diathesis. Heavier bleeding occurs in 5 to 25% of the operated

patients (blood loss of more than 5 ml/kg per hour). In cases with postoperative bleeding from the operation area one has to decide whether the hemorrhage is due to special circumstances in the operation area or inadequate surgical hemostasis, or whether and to what extent a disorder of hemostasis is causally responsible. Local fibrinolysis cannot be demonstrated by coagulation analysis on the systemic blood. Hemorrhages due to the surgical operation are often combined with coagulation disorders, making it difficult to decide for or against a repeat operation. Apart from the coagulation analysis findings, the clinical situation must also be taken into account in making the decision. A diffuse tendency to bleeding, a state of shock and the need for multiple transfusions argue in favor of a defect of hemostasis.

For blockade of the fibrinolysis it is recommended that 4 to 6 g of epsilon-aminocaproic acid should be given immediately postoperatively, in cases of hyperfibrinolysis 10 to 20 g of epsilon-aminocaproic acid/24 h or 1.0–3.0 g AMCHA (Ugurol)/24 h. Caution is advisable if circulatory insufficiency is present. Alternatively aprotinin (Trasylol) can be considered in a dose of 500000 KIU to 3 million KIU/day.

The prophylactic administration of Trasylol, which commences preoperatively and is continued with for 3 days (3 million KIU perioperatively, then 1.5–2.0 million KIU per day), significantly reduced the postoperative blood loss. Fresh plasma given at the end of the surgical operation is particularly suitable for correcting the defect of hemostasis because of its content of nonactivated coagulation factors and inhibitors of coagulation and fibrinolysis. It is recommended that during the postoperative period, especially if a consumption reaction is present, heparin should be infused in a dosage of 15000 IU to 20000 IU/day (corresponding to ca. 200 to 300 U/kg bodyweight and day). Factor concentrates are only justified in exceptional cases.

Massive Transfusion

By massive transfusion is meant a rapid single transfusion of 2500 ml and/or the transfusion of 5000 ml of whole blood within 6 to 24 h, and by rapid transfusion is meant the administration of about 100 ml of blood/min. The coagulation disorder which occurs during multiple transfusions depends:

1. on the nature and amount of the transfused whole blood, of the blood fractions and also the additionally infused plasma replacement substances (dextrans, hydroxyethyl starches, gelatins) and crystalline solutions;
2. on the patient's own compensation mechanisms for a transfusion-induced disorder of hemostasis. Thus it is influenced by the primary disease, an existing state of shock, the RES function, a preexisting increase in turnover or a hemostatic disorder of some other kind. The coagulation analysis to determine localization is not easy. As a rule the hemostatic disorder can only be classified with the help of the clinical picture and the course of the condition (Fig. 12).

The influence which can be expected on hemostasis can be deduced from the composition and age of the available blood products and fractions. ACD whole blood is stored for up to 21 days. Fresh blood is considered to be warm blood if it is not cooled after being taken and is transfused within 4 hours as far as possible. The thrombocytes and clotting factors are completely functional. Blood stored for up to 3 days is described as fresh blood; it should not be more than 6–7 days old. The hemolysis increases greatly from the 9th day. With transfusion after 21 days only 70% of the erythrocytes can still be demonstrated in the recipient blood 24 h after transfusion, for which a normal life-span can be assumed. ACD blood is diluted 1:4 and thus has a lower amount of hemoglobin and protein than normal blood. After 24 to 72 h the coagulation Factors V and VIII have fallen to below 50% of the norm through proteolytic degradation. Fibrinogen undergoes progressive degradation with the occurrence of split products. The

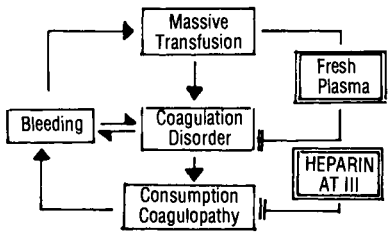

Fig. 12. Relationships between massive transfusion and coagulation disorder and the therapeutic influence of fresh plasma, heparin and antithrombin III (AT III)

prothrombin complex remains functional for a long time, but its activity also falls, especially that of Factor II. Only 20–30% of Factor XIII can still be demonstrated after 3 days. The content of inhibitor is reduced. The functional capacity of the thrombocytes is reduced after 3 h and has largely been extinguished after 48 hours. There are no thrombocytes in blood stored for more than 7 days; platelet aggregates can be demonstrated. Lipids with a procoagulatory potency are released from thrombocytes and erythrocytes.

In fresh blood (450 ml) with a normal thrombocyte count ($225000 \pm 75000/mm^3$), $1.0 \times 10^{11} \pm 0.3 \times 10^{11}$ thrombocytes are found. In platelet-rich plasma (220 ml) which is fresh and is not older than 4 h, 0.7 to 0.9×10^{11} thrombocytes can be demonstrated. In platelet concentrate (20–50 ml) 0.5 to 0.7×10^{11} thrombocytes are found. If no increased turnover is present the half-life of thrombocytes in the patient's plasma after 4 to 5 hours of storage amounts to 4.6 days with a recovery of 34%; after storage for 24 h at room temperature the half-life lies at 2.7 days with a recovery of 20%. Platelets transfused within 6 h are said to retain their function in vivo for 48 to 72 h.

A total of 100 to 150 ml of plasma citrate mixture are taken from an erythrocyte preparation. The hematocrit lies between 60 and 70%. The thrombocytes and leukocytes are not removed. Erythrocyte concentrate has a hematocrit of 70 to 80%, contains all the thrombocytes and leukocytes and has a plasma component of 15%. Through removal of the so-called buffy coat the thrombocyte and leukocyte count falls to below 10% of the original preparation, the plasma component lies at 1%. Washed erythrocytes no longer contain any thrombocytes and leukocytes and the plasma component lies below 18%. The coagulation-active plasmatic and corpuscular components progressively decrease in correspondence with the treatments described.

Fresh plasma should be transfused within 4 h after the blood has been taken. The clotting factors, the inhibitor potential and the thrombocytes are functional and present in normal concentrations. Fresh frozen plasma should be frozen within 4 h.

The massive transfusion of whole blood has metabolic and hemodynamic effects on the body through overloading with citrate, initial acidosis and later alkalosis, a possible hyperkalemia, the rise in lactate, through the reduction of 2,3-diphosphoglycerate of the circulating erythrocytes with increased oxygen affinity and through blood which is infused too cold with vasoconstriction and cardiac arrhyth-

mias. As already mentioned stored whole blood does not contain any material with a hemostatic action. With the progressive increase in the amount transfused a dilution and washout effect occurs leading to a fall in all the coagulation factors and in the thrombocytes and thus to a progressive defect of hemostasis which ultimately becomes a manifest hemorrhagic diathesis. A hemorrhagic diathesis regularly occurs after 15 transfusions; the thromboplastin time and the partial thromboplastin time become increasingly prolonged. If more than 15 transfusions of whole blood are needed, as far as possible only blood which is up to 24 h old should be used. The hemostasis defect which is induced through dilution is subsequently overlaid by an increase in turnover. Thrombocyte aggregates obstruct the pulmonary circulation and the systemic peripheral vascular region and lead to the picture of so-called transfusion lung. The use of microfilters (pore size 25–40 μ) instead of the previously used filters (pore size 170 μ) is essential. In circulatory shock in particular, heparinization is necessary (ca. 7500 to 15000 IU heparin/24 h). No microfilters need be used when fresh blood or fresh plasma are transfused. Heparinization should be carried out after 6 to 8 transfusions of whole blood.

For massive transfusions the administration of whole blood has been replaced by transfusions of erythrocyte concentrates and fresh plasma adapted to the situation. After 3–4 units (U) of erythrocyte concentrates it is advisable to give 1 U fresh plasma. One unit of a clotting factor per kilogram bodyweight (1 U corresponds to 100% activity of the clotting factor in 1 ml plasma) increases the factor concentration in the recipient plasma by about 1–2%. In some cases a moderate consumption reaction can already be compensated for with 500 ml to 750 ml of fresh plasma. If it is a case of hemorrhage following anticoagulation with coumarin derivatives, 6 to 8 day old blood is sufficient, because the factors of the prothrombin complex are relatively stable. Thrombocyte substitution is not necessary except for thrombocytopenic hemorrhage (leukoses, panmyelophthisis). As a rule fresh blood does not lead to a distinct rise in the thrombocyte count. A hemostatic effect is nevertheless observed with the transfused, functional thrombocytes. Thrombocyte counts of between 60000 and 90000/mm^3 are sufficient. If thrombocytes are needed, an effect can be achieved with 4 to 8 U of platelet-rich plasma and 8 to 16 U of platelet concentrate. A further transfusion is necessary after 1 to 3 days.

The disorder of hemostasis due to the transfusion can be complicated by the primary disease. Following multiple trauma, fat embolism and circulatory shock an activation of coagulation is induced, which can lead via a hypercoagulability into a consumption coagulopathy. The clearance capacity of the RES is reduced in these cases. In cases of hemorrhage erythrocyte concentrates and fresh plasma or freshly frozen plasma are indicated. Concomitant heparin therapy is generally necessary (Table 11). The shock must be combated first of all and once this has been achieved the disorder of hemostasis induced by the shock also regresses. The therapist often finds himself confronted by a vicious circle, in which a hemorrhage leads to circulatory shock and this in turn aggravates the tendency to bleeding through a disorder of coagulation with consumption coagulopathy (Fig. 6). A hypercoagulability is present in patients with tumors, sepsis and during the postoperative phase. Fibrinolysis may predominate during operations on the prostate and lungs. If hemorrhage develops in hemophilia, the transfusion concept is modified through the additional administration of appropriate factor concentrates. If hemorrhage develops during anticoagulation with coumarin derivatives, adjuvant therapy with prothrombin complex preparations may be necessary. The same applies to the hemorrhage of esophageal varices or bleeding from the intestinal tract in patients with hepatic cirrhosis.

If fresh blood or fresh plasma are not available in adequate amounts, one is forced to give Cohn's fraction I, cryoprecipitates, prothrombin complex and fibrinogen if the hemostatis potential has been exhausted. These should be given cautiously and with simultaneous heparin protection, because procoagulatory material is transfused. It is sufficient to transfuse up to the minimally effective concentration of the factors. Complete replacement of the coagulation potential is not necessary and is associated with additional risks in respect of the induction of a consumption coagulopathy and disseminated intravascular coagulation. Antifibrinolytics are indicated only if a distinct increase in fibrinolysis is demonstrated and if local activation of fibrinolysis is to be assumed in the region of extensive wound surfaces of organs rich in activator, such as the lungs, pancreas, pleura, uterus and prostate. Aprotinin is to be preferred to epsilon-aminocaproic acid and similar preparations.

Hemorrhagic Diathesis in Monoclonal Gammopathies

Occasionally hemorrhagic diatheses are observed in multiple myelomas and Waldenström's macroglobulinemia. Apart from patients with prolonged bleeding times, the degree of propensity to bleed is only loosely connected with the altered coagulation analysis parameters. The changes in the coagulation system show a certain relationship with the degree of paraproteinemia. Prolongation of the thrombin time takes the most important place. It can be explained as an antithrombin effect and/or as interference of the paraproteins with fibrin polymerization. Prolongation of the thromboplastin time and the partial thromboplastin time, and also a moderate decrease in individual coagulation factors occur. Functional defects of the thrombocytes have been described, accompanied by decreased adhesion and aggregation of the thrombocytes and a longer bleeding time. Therapy consists of treating the basic disease.

Immunocoagulopathies

Immunocoagulopathies are acquired coagulation defects. They occur as a rule in the course of substitution treatment for a congenital hemorrhagic diathesis. On account of the frequency of hemophilia A, antibodies against factor VIII predominate, and in the second place, in hemophilia B, those against factor IX. Their origin, clinical aspect, diagnosis and treatment have been described earlier. Antibodies have also been found in treatment for congenital formation defects of factors I, V, XI and XIII. Antibodies with corresponding hemorrhagic diathesis occur even in people who are not primarily hemophilia patients. They are observed in patients with autoimmune diseases in which immunological processes are involved, such as collagenosis, bronchial asthma, ulcerous colitis, regional enteritis, arteritis, after penicillin treatment and diseases of the lymphoreticular system. After pregnancy – 1 week to 1 year after the birth of the child – and in elderly people, inhibitors appear, mainly against factor VIII, spontaneously and without any recognizable cause. The antibodies belong mainly to the IgC class. In lupus erythematodes disseminatus an acquired antibody against prothrombin activator complex consisting of factor Xa, factor V and phospholipid has been described. It belongs to the

immunoglobulin class IgG or the IgA and IgM fraction. Most patients with so-called "lupus anticoagulans" have no tendency to bleed. Even thrombo-embolic complications can be observed. A hemorrhagic diathesis occurs only when a second hemostatic defect is present. In the rare cases of acquired von Willebrand-Jürgens syndrome an inhibitor against the factor VIII antigen has been identified.

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V. Thrombocytic Hemorrhagic Diatheses

Introduction

Most hemorrhagic diatheses are platelet dependent (Table 1). They are due to quantitative and/or qualitative changes in platelet production (production disorder). There may be reduced formation (thrombocytopenia), increased production (thrombocytosis or thrombocythemia), or functional defects (thrombocytopathy). They can also be congenital or acquired. There can also be increased platelet turnover (turnover disorder), which can be the cause of a hemorrhagic syndrome. With a few exceptions, turnover increases are acquired during life. Hemorrhagic syndromes arise with platelet counts less than 10000 to 30000 per mm^3. If there is in addition a functional defect in the platelets, one can get such a syndrome at higher counts. Thrombocytopathies also lead to a tendency to bleeding with normal or even elevated platelet counts. In the congenital thrombocytic hemorrhagic syndromes, no causal treatment is possible. In most cases, the bleeding can be offset by treating the underlying disease. Therapeutic measures particularly directed to the platelets are based on the administration of corticosteroids, splenectomy, and bridging emergency situations by platelet transfusion. Corticosteroids are given in thrombocytic hemorrhagic syndromes in which immune processes are involved and which are not the consequence a congenital production disturbance. A daily dose of from 50 to 150 mg of prednisolone or an equivalent dose of an analogous drug in the initial phase can subsequently be reduced to a maintenance dose. Splenectomy can be necessary if the steroid treatment is unsuccessful and the main region of platelet destruction is indicated by isotope studies as being the spleen. Platelet transfusions

Table 1. Occurrence of quantitative and qualitative congenital and acquired disorders in platelets with hemorrhagic diathesis and thrombosis

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Thrombocytopenias

A. Production disorders
   1. Congenital
      a) Fanconi syndrome (constitutional pancytopenia)
      b) Amegakaryocytic thrombocytopenia with radius aplasia
      c) Wiskott-Aldrich syndrome
      d) May-Hegglin anomaly
      e) Thrombopoietin deficiency
      f) Bone marrow infiltration (congenital leukemia)
      g) German measles in neonates
      h) Consequences of maternal intake of thiazide diuretics
   2. Acquired
      a) Aplastic anemia
      b) Megakaryocyte aplasia
      c) Bone-marrow infiltration (carcinoma, leukemia, etc.)
      d) Ionizing radiation
      e) Drug toxicity bone-marrow depression
      f) Cyclic thrombocytopenia
      g) Vitamin B 12 deficiency, folic acid deficiency, etc.
      h) Virus infections
      i) Paroxysmal nocturnal hemoglobinuria
      j) Chronic kidney insufficiency

B. Turnover disorders
   1. Congenital
      a) Nonimmunological
         I. Fetal erythroblastosis
         II. Premature birth
         III. Infection
         IV. Hemangioma
      b) Immunological
         I. Drug hypersensitivity
         II. Maternal idiopathic thrombocytopenia purpura
   2. Acquired
      a) Nonimmunological
         I. Infection
         II. Disseminated intravascular coagulation
         III. Thrombotic-thrombocytopenic purpura
         IV. Hemolytic-uremic syndrome
         V. Drug induced
         VI. Hypersplenism
         VII. Bleeding
         VIII. Extracorporeal circulation

Table 1. (Continued)

b) Immunological
   I. Antilymphocyte serum
   II. Drug induced
   III. Posttransfusional purpura
   IV. Idiopathic thrombocytopenic purpura (acute, chronic)

Thrombocytopathies
1. Congenital
   a) Bernard-Soulier syndrome
   b) Glanzmann-Naegeli thrombasthenia
   c) Hereditary macrothrombocytopathy with nephritis and deafness
   d) Platelet factor 3 deficiency
   e) Storage-pool defect
   f) Aspirin-like disease
2. Acquired
   a) Drug induced
   b) Uremia
   c) Liver diseases
   d) Myeloproliferative diseases
   e) Various

Thrombocytoses
1. Primary
   a) Thrombocythemia
   b) In combination with other myeloproliferative diseases
2. Secondary
   a) Acute and chronic inflammatory diseases
   b) After acute bleeding
   c) Iron deficiency
   d) Hemolytic anemia
   e) Neoplasias (paraneoplastic)
   f) Postoperative

can be used to alleviate massive thrombocytopenia and to bridge phases of life-threatening hemorrhagic syndromes. If the antigen systems are different (ABO blood groups or HLA system), antiplatelet antibodies develop after a certain time, which eliminates any value from the platelet transfusion. In thrombocytopenia of immunologic origin, the value of platelet transfusion is restricted by the short circulating survival time. The tendency to bleeding is characterized by the thrombocytic bleeding type, with the occurrence of pinhead to

lentil-size petechiae in the skin, mucosae, serous membranes, meninges, and parenchymatous organs. The lower extremities are particularly affected as regards the skin. One gets epistaxis, gingival bleeding, intestinal bleeding, and hematuria, and also (in women) menorrhagia and metrorrhagia. Joint bleeding is rare. On account of the involvement of platelets in the regular course of intrinsic clotting, there can also be involvement of the plasmatic components in hemostasis in thrombocytopenia and thrombocytopathies, with the occurrence of ecchymoses and suffusion.

Thrombocytopenias

Congenital Production Disorders

Fanconi Syndrome

The Fanconi syndrome in based on bone-marrow aplasia. Thrombocytopenia occurs in the neonatal period and in early childhood. Pancytopenia occurs some years later. There is very little effect on the thrombocytopenia from steroids, androgens, and splenectomy. The hemorrhagic syndrome is the most frequent cause of death, after infections. The syndrome is combined with malformations and is inherited in an autosomal recessive fashion.

Amegakaryocytic Thrombocytopenia with Radius Aplasia

The syndrome is inherited in an autosomal recessive fashion. In addition to thrombocytopenia, there is bilateral aplasia in the radii. Heart defects and other malformations occur. The platelet count is in part very much reduced, while the lifetime is usually normal. Few or no megakaryocytes are detectable in the bone marrow. The hemorrhagic syndrome occurs frequently even in the first week, and is usually manifest before the fourth month of life. Many of the infants die during the first year, frequently from cerebral hemorrhage. If they survive the first year, the prognosis is better. Severe hemorrhage can be treated with platelet transfusion. Splenectomy and corticosteroids are of no value. Leukemoid reactions can occur.

Wiskott-Aldrich Syndrome

The syndrome is recessively inherited on the X chromosome. It occurs in male neonates and is characterized by thrombocytopenia, eczema, and an elevated liability to infection. Hemorrhage usually occurs within the first six months of life. Most often the children die before the age of 10 from the hemorrhagic syndrome or from overwhelming infections. There are T-cell and B-cell deficiencies in the lymphocytes. The platelets are smaller than normal. The megakaryocyte count in the bone marrow is normal or elevated. The platelet lifetime is shortened. Homologous normal platelets have normal lifetimes. From this it has been concluded that there is a congenital platelet defect. Platelet aggregation and other functional tests are abnormal. Corticosteroids and splenectomy are unsuccessful. Treatment with transfer factor appears able to raise the platelet count. The ultrastructure of the platelets shows anomalies.

May-Hegglin Anomaly

This anomaly is inherited as an autosomal dominant and is characterized by thrombocytopenia of variable extent, with giant platelets as well as basophilic inclusion in the granulocytes (Döhle bodies). The megakaryocyte count in the bone marrow is normal. The hemorrhagic syndrome is expressed to variable extents. Normal and shortened platelet lifetimes may be measured with autologous platelets. The treatment is with corticosteroids, or with platelet transfusion in more severe hemorrhagic diathesis.

Various

Familial thrombopoietin deficiency has been described in a single case while hereditary thrombocytopenia with macrothrombocytes occurs with the Alport syndrome (hereditary nephritis and deafness) along with unclassifiable thrombocytopenias, which are rarities.

Acquired Production Disorders

Acquired thrombocytopenia occurs as a consequence of reduced bone-marrow production mainly in adulthood. This is usually associated with simultaneous depression in erythropoiesis and granulopoiesis. Clinical symptoms appear only in advanced stages. The first signs are weakness on account of anemia, tendency to infection as a consequence of leukopenia, or hemorrhagic diathesis of thrombocytic type with thrombocytopenia. The causes to be considered are *idiopathic panmyelopathy* or *secondary bone-marrow damage* of various origins. The bone marrow either lacks megakaryocytes completely or shows very much reduced numbers. In secondary bone-marrow damage, one has to consider marrow infiltration in carcinosis and leukosis or myelosuppressive substances of different types. Toxic drug bone-marrow depression occurs with thrombocytopenia as a consequence of treatment with cytostatic drugs, antibiotics (chloramphenicol, sulfonamides, streptomycin, penicillin, and amphotericin B), phenylbutazone, thiazides, oral antidiabetic drugs (carbutamide, tolbutamide), and antihistamines. Thrombocytopenia is also observed after exposure to benzene or ionizing radiation, and after acute or chronic alcohol abuse, after virus infections (hepatitis, measles, German measles, influenza, infectious mononucleosis, and dengue fever), as well as bacterial infections (miliary tuberculosis), after treatment with estrogens (diethylstilbestrol), and in certain metabolic disorders (iron deficiency, vitamin B_{12} deficiency, vitamin C deficiency). *Cyclic thrombocytopenia* of uncertain cause occurs in women before the menopause with a time relationship to the menstruation cycle. However, it also occurs in women after the menopause and sometimes in men. Chronic thrombocytopenia is observed in *paroxysmal nocturnal hemoglobinuria.*

The treatment is adjusted to the underlying disease and may involve eliminating the causative noxae. Temporary measures are provided by corticosteroids and platelet transfusion if there is severe hemorrhagic diathesis.

Turnover Disorders

Idiopathic Thrombocytopenic Purpura (ITP) or Werlhof's Disease

Definition and Pathogenesis. There are differences in clinical course and probably also in pathogenesis between the acute and chronic forms of thrombocytopenic purpura. Both forms are characterized by reduced platelet count as a consequence of increased platelet destruction and thus shortened platelet lifetime. The megakaryocyte count in the marrow is normal or elevated. The morphology of the megakaryocytes is different from that in the normal. The tendency to hemorrhage varies. Idiopathic means that an exclusion diagnosis is involved. The etiology is uncertain. Acute ITP occurs mainly in childhood, and is frequently due to virus infection. The thrombocytopenia lasts for a few weeks to months. Chronic ITP occurs mainly in adulthood and is found with variable extent for years and does not usually clear up spontaneously. An autoimmune process has been considered as responsible for the thrombocytopenia. ITP also occurs more frequently with autoimmune hemolytic anemias. The transfusion of ITP plasma into healthy subjects induces a transient thrombocytopenia. The lifetime of transfused and isotopically labeled isologous platelets of the same blood group is shortened to a few days or even hours. The destruction occurs mainly in the reticuloendothelial system of spleen and liver. The postulated antibodies can be adsorbed on platelets and can also be eluted from platelets, spleen, and liver, but they have not yet been characterized precisely. They appear to be constituted by a 7S gammaglobulin.

Clinical Features and Diagnosis. The frequency is quoted as from 0.012 to 0.18% in the population. The proportion of ITP in the total of thrombocytopenias appears to be 5 to 10%. Acute ITP affects mainly children of age two to nine, although it can occur at any age. In 80%, there is acute infection, mainly a virus disease. The thrombocytopenia follows the infection with an interval of two days to three weeks. It can also occur after active immunization against measles, mumps, and chicken pox. The onset is abrupt, as is the spontaneous recovery after a few weeks to months.
Chronic ITP can also occur in adolescence, but about 80% of the cases

occur between the ages of 20 and 50. 75% of the cases are women. A preceding infection is rarely observed.
Thrombocytopenic hemorrhage occurs in acute and chronic ITP. One finds petechia on the mucosae and skin, particularly in the dependent parts of the body. However, gastrointestinal and intracerebral hemorrhages are rare. The hemorrhage sets in suddenly in acute ITP and decreases a few days later, while in chronic ITP, the diathesis is more commonly in milder form and occurs over months or years. Joint bleeding is rare. There is increased hemorrhage following operation or trauma.
The diagnosis is based on the clinical course and by the exclusion of other thrombocytopenias. The platelet count is reduced to between 5000 and 20000 per mm^3 during the acute phase, while in chronic ITP, one finds values of about 75000 per mm^3, namely somewhat higher than in acute ITP. The bleeding time is lengthened. The Rumpel-Leede and pinch provocation tests are pathological. The megakaryocytes in the bone marrow are normal to increased and show shape deviations from normal. The platelet lifetime is reduced to a few days or hours. The main site of destruction is the spleen, with the liver coming second.

Treatment and Course. Most patients recover spontaneously from acute ITP. Steroid treatment appears to be necessary only in a few cases with pronounced thrombocytopenia. In chronic ITP, some 10 to 20% of adults recover spontaneously. If the hemorrhage is life-threatening, platelet transfusion is indicated, although the effect is at present very restricted on account of antibody-induced shortened lifetimes. If there is pronounced thrombocytopenia with hemorrhagic diathesis, one gives steroids in amounts of from 0.5 to 3 mg of prednisolone per kg in decreasing doses. The platelet rise from steroids occurs within two to three weeks. Patients who do not respond suitably to steroids and who show predominant platelet destruction in the spleen may require splenectomy. In 70 to 90% of patients, the platelet counts increase within 24 h or one to two weeks. Even if the response is inadequate, the background for steroid treatment can be improved after splenectomy. Patients who do not respond to steroid treatment and/or splenectomy may be treated with immunosuppressive drugs. One mainly uses azathioprine (Imurek) in a dosage of 100 to 300 mg/d, as well as cyclophosphamide (Endoxan) in a dosage of 100 to 200 mg/d,

with or without simultaneous steroids. In individual cases, one can use vincristine. Success in chronic ITP is to be expected in from 15 to 35% of cases. The delay before there is a platelet rise can be as much as six months. It appears of no value to treat by transfusion with platelets that have been treated with Vinca alkaloids. Children and adults show temporary platelet rises lasting for one to three weeks following intravenous administration of polyvalent 7S IgG in doses of 0.2–0.4 g/kg body weight per day for five days. The thrombocytes increase after 1–2 days and reach normal levels after 4–5. The bleeding time becomes normal. The following have been discussed as possible mechanisms: possible elimination of circulating immune complexes or viruses, competitive inhibition of the adsorption of plasma immunoglobulins or immune complexes on the platelets, and competitive inhibition of platelet elimination by temporary RES blockade.

The *Evans Syndrome* is characterized by the simultaneous occurrence of thrombocytopenia and autoimmune hemolytic anemia. It is considered that autoantibodies are responsible for the thrombopenia. The thrombocytopenia can precede the anemia. The acute or chronically recurrent course is similar to that of ITP.
Thrombocytopenia occurs in one-third of patients with *lupus erythematosus*. It is assumed that an autoimmune mechanism is responsible for the thrombocytopenia. Immune hemolytic anemias are relatively common. The clinical picture of the thrombocytopenia is the same as in ITP.
The treatment of the Evans syndrome and of the thrombocytopenia in lupus erythematosus is the same as that in ITP.

Thrombocytopenias due to Antigen-Antibody Reactions

The interaction of immune complexes with platelets leads to the activation of the latter, which show release reaction and increased destruction. This immunological thrombocytopenia is produced in nearly all cases following drug sensitization. In previous immunization of passive type, which may involve the repeated injection of foreign protein (serum disease), one can get an acute thrombocytopenia, and the same can occur from food allergy. Nearly all drugs can produce this

effect. We may mention particularly analgesics (salicylates, acetyl salicylic acid, phenylbutazone, etc.), antibiotics (penicillins, tetracyclines, sulfonamides, rifampicin, etc.), quinone alkaloids (quinine, quinidine), sedatives, hypnotics, and anticonvulsants (allylisopropylacetylurea = Sedormide, barbiturates, diphenylhydantoin, meprobamate), sulfonamide derivatives (acetazolamide, chlorpropamide), furosemide, and digitoxin.

The platelet activation with the release of coagulation-stimulating substances can attain a scale such that there is generalized intravascular activation of the clotting system with consequent consumptive reaction. The thrombocytopenia occurring following kidney transplantation is probably of the same origin. The thrombocytopenia occurs in most cases within 24 h of taking the drug. The platelet count falls to 20000 per mm^3 of less. One cannot distinguish the thrombocytopenic hemorrhagic diathesis from that occurring in ITP. With drugs that are eliminated rapidly, the hemorrhagic diathesis disappears after three to four days. The plasma contains antibodies that act together with the causative drug to cause platelets to aggregate, and also produce lysis, complement fixation, and the release of platelet contents. The marrow megakaryocytes are normal.

The treatment consists of eliminating the allergen. Corticosteroids do not shorten the thrombocytopenic phase, although they have a positive effect from a possible reduction of vascular permeability. Platelet transfusions are unsuccessful, because there is rapid intravascular destruction. Acute bleeding complications can be overcome by exchange transfusion or plasmapheresis.

Posttransfusional Purpura

The syndrome occurs in people who have been immunized by previous blood transfusions and in women who have been immunized against platelet isoantigens on account of pregancy. This involves mainly platelet antigen PL_{A1}, which is present in 98% of the population. It is lacking in people who develop posttransfusion purpura. The antibodies produced against the donor platelets following transfusion are also directed against the patient's own platelets. About a week after renewed transfusion, one gets destruction of the patient's own autologous platelets, with thrombocytopenia of 10000 per mm^3 or less,

together with the corresponding hemorrhagic syndrome. The thrombocytopenia recovers spontaneously after 10 to 48 days. Platelet transfusion and steroids are without effect. Acute bleeding complications can be offset by plasmapheresis or exchange transfusion.

Thrombocytopenias of Various Origins

Thrombocytopenia can occur as a parainfectious or postinfectious process. This may be due not only to production disorder or antigen-antibody reactions but also to the infectious agent having a direct damaging effect on the platelets. This is more common in childhood and rarer in adults. Thrombocytopenia is found in the following circumstances amongst others: following infectious mononucleosis, German measles, varicella, mumps, cytomegaly, hepatitis, and malaria. It sets in about one week after the start of the disease and can last for several weeks. It also occurs during septicemia, mainly as caused by gram-negative bacteria, but also by gram-positive ones. There are transient transitions to the syndrome of disseminated intravascular clotting and consumptive coagulopathy, which are mentioned elsewhere. The above statements apply to the treatment.
Thrombopenia occurs following extracorporeal circulation and dialysis on account of mechanical damage to the platelets, and also during heparin treatment, in certain endocrine disorders (Cushing's disease and hyperthyroidism), in hypersplenism, and as a consumptive thrombocytopenia in hemangiomas in the liver, spleen, and brain (Kasabach-Merritt syndrome). In the last case, heparin is of therapeutic value.

Thrombotic Thrombocytopenic Purpura (TTP)

Definition and Pathogenesis. The syndrome was first described in 1925 by Moschcowitz. The etiology is uncertain. One finds disseminated endothelial damage and defects in the arterioles and capillaries of numerous organs. Inflammatory vascular changes are rarely or never observed. The endothelium in the major vessels is unaltered. Syndromes resembling TPP occur during immunological diseases such as disseminated lupus erythematosus and rheumatoid arthritis, so it is

assumed that there is a relationship to immunological processes, although this has not been confirmed. The disease sometimes occurs following bacterial and viral infections. One finds hyaline microthrombi in the region of the vascular damage, which consists mainly of platelets and to a minor extent of fibrin, which presumably comes from the platelets. The endothelial plasminogen activator is not detectable or only slightly so in the region of the vascular lesions. Locally activated fibrinolysis is therefore not possible and would also be largely ineffective, since the thrombi consist largely of platelets. One finds reduced prostacyclin production in the vessel walls, which on account of reduction in the antiaggregatory principle shifts the postulated equilibrium between proaggregatory thrombocytic thromboxane production and antiaggregatory endothelial prostacyclin production, thus producing an elevated tendency to platelet thrombus production. As therapeutic success is obtained with plasma transfusion, it is postulated that there is a lack of a aggregation inhibiting factor. Descriptions have been given of elevated aggregation tendencies of platelets in TPP patients.

Clinical Features and Diagnosis. The clinical symptoms are to be seen as consequences of the vascular damage, with diffuse platelet thrombus production. The symptoms are characterized by five aspects, which consist of thrombocytopenia, neurological disorders, microangiopathic hemolytic anemia, renal insufficiency, and fever. The last two symptoms are either not predominant or even not detectable in numerous patients. The thrombopenia may attain values of less than 50000 per mm^3. One finds petechial hemorrhagic symptoms in the skin and mucosae, with gastrointestinal, urogenital, and nasopharyngeal bleeding tendencies. A consequence of the hemolysis, with the occurrence of fragmentocytes, is anemia, which may attain values less than 5 g% and be accompanied by icterus. The kidney insufficiency can make dialysis necessary. The neurological symptoms consist of a paresis, paresthesia, and cerebral symptoms extending as far as unconsciousness. Muscle pains and abdominal and thoracic pains have been observed.

The disease picture is usually relatively acute, and it mainly affects people between the ages of 10 and 40, with a preference for the third decade and for the female sex. TTP can also occur directly up to several months postpartum.

Laboratory tests show thrombopenia, hemolytic anemia with fragmentocytes, reticulocytosis, leukocytosis, and hyperbilirubinemia. The Coombs test and the LE cell phenomenon are negative. The platelet and erythrocyte lifetimes are shortened. There are no signs of disseminated intrasvascular coagulation with falls in fibrinogen and other clotting factors.
Difficulties occur in differential diagnosis in the case of isolated thrombocytopenia in the course of autoimmune disease and microangiopathic hemolytic anemias of other origins. In sepsis, one can find isolated thrombocytopenia with normal fibrinogen concentrations and normal activity for the other clotting factors, which can involve difficulties in differential diagnosis. In such cases, however, there are close relationships to consumptive coagulopathy, together with typical clotting-disturbance patterns usually arising in the subsequent course. See below for the relationship to hemolytic uremic syndrome.

Treatment. The most effective treatments appear to be transfusion with fresh plasma or fresh frozen plasma. Insofar as there are no volume problems, one can recommend from six to 10 units within the first 24 h; on the subsequent days, a therapeutic effect is produced by up to three units a day. If there is deterioration after stopping the treatment, the therapy can be repeated. Alternatively, one can recommend exchange transfusion and plasmapheresis. High-dosage corticosteroids and splenectomy may need to be considered in each case. Heparin treatment is ineffective on account of the lack of a relationship between the plasmatic clotting system and the mainly thrombocytic components of the thrombi, and it is not indicated on account of elevated bleeding hazard, the same applying to fibrinolysis treatment. At present, we do not have sufficient experience with the effects of infusion of prostacyclin or analogous drugs (prostacyclin dose 8–15 ng/kg per minute). Platelet clumping inhibitors have several times been tested, but without provision of any exact statements on the usefulness. The mortality is high, particularly if cerebral symptoms occur or renal insufficiency requiring dialysis.

Hemolytic Uremic Syndrome (HUS)

Gasser in 1955 described this syndrome, which has close clinical and pathological similarities to thrombotic thrombocytopenic purpura. It is suspected that the pathogenesis is not decisively different. The syndrome occurs mainly in children before the age of eight, particularly below the age of one, being rare in adults. It has also been observed in women from a few days to several months postpartum and has occurred in relation to malignant hypertension and following kidney transplantation.
One finds endothelial damage in the glomerular capillaries and the renal arterioles, with local deposition of platelet-fibrin thrombi. Sometimes, the condition is preceded by a viral or bacterial infection. The picture is characterized by thrombocytopenia, microangiopathic anemia, fever, renal failure, and relatively often by associated hypertension. Neurological manifestations and liver involvement are relatively rare. The mortality is 5% in children without renal involvement. The treatment is symptomatic with hemodialysis, blood transfusion, and antihypertensive treatment. There is a controversy about administering heparin. There have been some isolated reports of positive results with inhibitors of platelet function.

Thrombocytopathies

Introduction

Disorders in platelet function may be congenital or acquired. Congenital thrombocytopathies are relatively rare, whereas acquired disorders are common and have been observed during various underlying diseases and following the administration of numerous drugs. The type of bleeding may vary, with the occurrence mainly of skin and mucosal bleeding in the form of purpura and of petechia not of a hemorrhagic diathesis in thrombocytopenia as well as with vascular bleeding tendency. One suspects thrombocytopathy whenever there is a corresponding clinical bleeding symptom pattern but the platelet count is normal or nearly so and there are no disorders in the plasmatic clotting system. In thrombocytopathies, one also gets activity reductions in various clotting factors, which are either obligatory and are respons-

ible for the thrombocytic defect (von Willebrand-Jürgens syndrome, afibrinogenemia) or else are not constant symptoms and can relate to various factors to different extents. Vascular hemorrhagic symptoms occur usually against a background disease, which can give diagnostic assistance. As there is functional unity between the vascular wall and the platelets, both systems may be affected. Elsewhere we describe platelet disorders in which the platelets themselves are intact but where the hemorrhagic diathesis arises from a plasma defect (von Willebrand-Jürgens syndrome and afibrinogenemia). The other congenital thrombocytopathies can be subdivided into ones in which the defect is localized in the membranes and ones that show intracellular abnormalities. It is not always easy to distinguish and diagnose the numerous functional disorders. This requires exact anamnesis, family history, definition of the bleeding type, and general examination. Further evidence is provided by platelet function tests (bleeding time, adhesion, and aggregation with numerous stimulants, Table 2 and Fig. 1). In individual cases, more laborious measures are necessary, such as release-reaction analysis, examination of the nucleotide and serotonin contents, and the functional capacity of the porstaglandin-thromboxane system.

Congenital Thrombocytopathies

Bernard-Soulier Syndrome

Definition, Etiology, and Pathogenesis. The syndrome was described in 1948 by Bernard and Soulier as a congenital hemorrhagic diathesis with prolonged bleeding time and characterized by giant platelets. It is inherited in an autosomal recessive fashion. The defect is defined biochemically by deficiency, lack, or functional disorder in the membrane-related glycoprotein I complex (glycoproteins Ia and Ib). The complex is responsible for the receptor function of the platelets. It is on the one hand necessary for the interaction of the platelets with the von Willebrand factor, which produces the linking to the subendothelial collagen in the primary hemostasis, and on the other for the aggregation induced by ristocetin. Therefore adhesion to the subendothelial tissue and aggregation by ristocetin fail. While the ristocetin-

Table 2. Diagnostic criteria in congenital disorders in platelet function (Hardisty and Caen 1981)

Disease	Platelet aggregation						Serotonin/ ADP release by thrombin	Heredity	Associated symptoms
	Platelet count	Platelet size	ADP	Collagen	Arachi-donic acid	Risto-cetin			
Glanzmann-Naegeli thrombasthenia	N	N	O	O	O	(1)	N	Autosomal recessive	
Bernard-Soulier syndrome	↓ (N)	↑	N	N	N	O	N ↓	Autosomal recessive	
Hermansky-Pudlak syndrome	N	N	(1)	↓	N	(1)	↓	Autosomal recessive	Albinism
"Storage pool" defect	N	N ↓	(1)	↓	N	(1)	↓	Autosomal dominant	
Wiskott-Aldrich syndrome	↓	↓		↓			↓	X-chromo-some recessive	Eczema, tendency to infection
Chédiak-Higashi syndrome	N ↓	N	(1)	↓			↓	Autosomal recessive	Partial albinism and tendency to infection
"Aspirin-like" disease	N	N	(1)	↓	↓		↓	?	
α-granule defect	↓	↑	↓	↓	N	N	↓	Autosomal dominant	

(1) Only in the first phase of aggregation

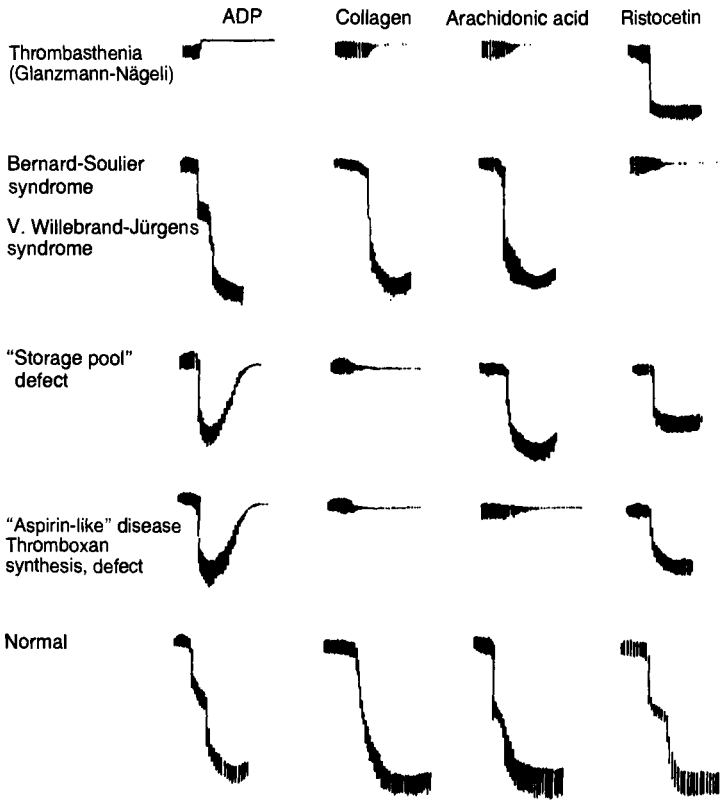

Fig. 1. Course of the aggregation curves in congenital disorders of thrombocyte function in comparison to the normal aggregation course after stimulation with ADP, collagen, arachidonic acid, ristocetin (Hardisty, Caen, 1981)

induced aggregation can be restored in the von Willebrand syndrome following suspension of the platelets in normal plasma on account of supplementation of the von Willebrand factor, this is not the case with the platelets in the Bernard-Soulier syndrome.

Clinical Features and Diagnosis. The syndrome cannot be distinguished from other congenital platelet function disorders on the basis

of the clinical symptoms. It is characterized by frequent superficial skin and mucosal bleeding in the form of ecchymoses, purpura, and petechiae. Posttraumatic and postoperative bleeding are prolonged and enhanced. Epistaxis, gastrointestinal bleeding, and menorrhagia can attain various scales. The hermorrhagic diathesis occurs in the first few weeks and months of life. The platelet count is normal or only slightly reduced; the bleeding time is lengthened. The clot retraction and the platelet factor 3 availability are normal. Prothrombin consumption is delayed. The platelets aggregate normally with ADP, adrenaline, and collagen. Platelet agglutination with ristocetin, bovine fibrinogen, and factor VIII is reduced or abolished. In contrast to the von Willebrand-Jürgens syndrome, normal plasma or factor VIII cannot correct the ristocetin-induced aggregation. The platelet retention is normal or reduced. The microscope reveals giant platelets. Heterozygotes are clinically normal and show no detectable platelet defect.

Treatment. Usually, local blood-stopping measures are sufficient. Platelet transfusions are necessary following injury and operation. It may be necessary to suppress menstrual bleeding. Steroids and splenectomy are unsuccessful.

Glanzmann-Naegeli Thrombasthenia

Definition, Etiology, and Pathogenesis. This platelet defect was first described in 1918 by Glanzmann. It is inherited in an autosomal recessive fashion. The defect is characterized biochemically by deficiency or complete lack of membrane glycoproteins IIb and IIIa. Fibrinogen, whose level in the platelets of patients with thrombasthenia is reduced, is necessary for normal platelet aggregation by ADP. It has been suggested that the deficiency of glycoproteins IIb and IIIa means that ADP is not in a situation to make the fibrinogen receptors on the platelet accessible. A deficiency of alpha-actinin in the platelets has also been described. ADP, adrenaline, thrombin, or collagen are bound in a normal fashion to the platelets. The subsequent shape change is normal, but the aggregation does not occur, which is due to the defect occurring in a later phase of the platelet function. The adhesion to the subendothelial collagen tissue is also

normal. On the other hand, the adhesion to and spread on glass and the retention in glass-bead columns are disturbed.

Clinical Features and Diagnosis. The hemorrhagic diathesis does not differ from that in other platelet function disorders, as it shows petechial bleeding tendencies in skin and mucosae, epistaxis, menorrhagia, and gastrointestinal bleeding, together with increased posttraumatic and postoperative hemorrhagia. The tendency to bleeding becomes manifest in the infant, and occurs to various extents, with a tendency to decrease as the age advances. The bleeding time is lengthened. Although one initially finds morphological changes, there is no aggregation with ADP, adrenaline, thrombin, or collagen, or with substances dependent on platelet ADP for normal aggregation. Aggregation can be induced by bovine factor VIII and ristocetin (first phase). The production of prostaglandin endoperoxides and thromboxane and the secretion of the contents of the dense bodies (nucleotides, serotonine) is normal following the administration of arachidonic acid, thombin, and ionophor A 23187, but not after ADP. The platelet factor 3 availability and the prothrombin consumption are perturbed. The platelet fibrinogen is reduced in 80% of cases. The clot retraction is also disturbed. The platelet lifetime is normal. Heterozygotes are symptomless.

Treatment. Most of the instances of bleeding can be treated with local measures. Severe hemorrhage is treated with platelet transfusion. Menorrhagia may require hormone treatment under certain circumstances. Splenectomy and steroids are not successful.

Hereditary Macrothrombocytopathy with Nephritis and Deafuess. Epstein in 1972 described this syndrome, which does not differ from the Bernard-Soulier syndrome as regards hemorrhagic picture, platelet morphology, and platelet function. The characteristics are the combination with hereditary interstitial nephritis and neurogenic deafness (Alport syndrome). The triad is inherited in an autosomal dominant fashion.

Platelet Factor 3 Deficiency. Platelet factor 3 is not a factor in the usual sense but rather an activity of the platelet membrane, which is made available in the release reaction and is of significance in the activation of plasmatic clotting factors during hemostasis. It is suspected that the interaction between the platelets, factor V, and factor Xa is per-

turbed. The platelet factor 3 availability in vitro following the addition of kaolin and ADP is reduced. The prothrombin consumption is also reduced. Aggregation, secretion, and bleeding time are normal. The hemorrhagic diathesis is expressed to a moderate extent. In addition to the isolated platelet factor 3 deficiency, one finds the defect also as a partial component in platelet function disorders of other origins.

"Storage Pool" Defect and "Aspirin-like" Disease

Introduction. While one can characterize the Bernard-Soulier syndrome and Glanzmann's thrombasthenia by a disorder in the first phase of ristocetin – or ADP – induced aggregation, one can detect inhibition of the second phase of aggregation and a lacking or restricted release reaction in thrombocytopathies with intracellular defects. Here one has a heterogeneous group of conditions that can occur either in isolation or in combination with other disturbances. Hardisty and Hutton in 1967 gave a description of a group of patients with relatively mild bleeding tendency but of whom many had prolonged bleeding times and whose platelets did not aggregate in response to collagen, while following ADP or adrenaline, there was only the first phase of aggregation without the subsequent second one. The release reaction was lacking. The functional defects have been further elucidated and characterized in recent years. They show extensive similarities in the clinical features and laboratory parameters, and they can be distinguished only by estimating the intracellular nucleotide contents.

"Storage Pool" Defect

Definition and Pathogenesis. The disease is inherited as an autosomal dominant trait. The defect is characterized by reduction in or lack of the dense bodies (beta granules). The storage capacity for ADP, ATP, calcium, and serotonin is depressed. The contents of these substances are reduced by comparison with normal platelets. The metabolic pool is not affected. As the storage organelles in healthy subjects contain relatively much ADP in comparison with ATP, the ratio of ATP to ADP is higher than normal in patients with storage-pool defect. Incubating the platelets with radioactive serotonin shows a normal initial uptake, but the uptake ceases soon at a low level. The degrada-

tion of serotonin in the cytosol is relatively rapid, since the protective function of the beta granules is not present. The prostaglandin metabolism is usually undisturbed. For this reason, the aspirin-like disease described below can be corrected by means of platelets with storage pool defect, and vice versa. Also, forms have been described of the storage pool defect in which there is reduced activation of phospholipase A_2 by ADP, collagen, and adrenaline, with reduced arachidonic acid release and reduced prostaglandin production. It is assumed that the explanation is a lack of ADP cofactor function for the prostaglandin synthetase. There have also been reports of associated disorders in the release reaction from the alpha granules and lysosomes.

Clinical Features and Diagnosis. The bleeding tendency is relatively slight, although it does not differ from that in the above platelet function disorders. The bleeding time is lengthened. The in vitro aggregation due to collagen is eliminated or very much reduced; with ADP and adrenaline, only the first phase of aggregation, with the release-reaction lacking, is observed. The platelet aggregates readily break up again. Aggregation is induced by the addition of arachidonic acid.

Treatment. Apart from local measures, treatment is not usually necessary. Following injury and operation, platelet transfusion restores the normal hemostasis. Although the platelet functional disorder persists, the bleeding time can be shortened by the administration of cryoprecipitate.

Hermansky-Pudlak Syndrome

This syndrome was described by Hermansky and Pudlak in 1959; it has autosomal recessive inheritance. Less than 50 cases have been documented in the world literature. The syndrome is characterized by a triad of life-long tendency to bleeding, tyrosinase-positive oculocutaneous albinism, and the presence of pigmented macrophages in the bone marrow. The platelet disorder corresponds to that described in the storage pool defect. The syndrome can be combined with lung fibrosis and inflammatory changes in the gastrointestinal tract.

Other diseases can also be combined with a storage pool disease. We may mention the autosomal recessive inherited *Chediak-Higashi syndrome,* in which abnormal granules in most of the granule-containing cells are detectable, and which is characterized not only by a hemorrhagic diathesis but also by partial oculocutaneous albinism and recurrent purulent infections. In the *Wiscott-Aldrich syndrome* and in *thrombocytopenia with radius aplasia,* one can also detect storage-pool defects.

Alpha-granule Deficiency ("Gray Platelet" Syndrome)

Individual cases have been described in which the microscope reveals only very few alpha granules, with a corresponding deficiency of platelet factor 4, beta-thromboglobulin, platelet fibrinogen, and platelet growth factor. The beta granules and lysosomes occur in normal numbers and have their normal contents. On account of the gray appearance of the platelets, the disease has been called the "Gray platelet" syndrome. It involves reduced aggregability in response to collagen, thrombin, adrenaline, and ADP. The prostaglandin metabolism appears to be unaffected. The precise pathogenetic mechanism is not clear.

"Aspirin-like" Disease

Definition and Pathogenesis. The disease takes it name from the similarity of the platelet disorder to that following the taking of drugs containing acetylsalicylic acid. This acid inhibits prostaglandin metabolism by acetylating cyclooxygenase. In the congenital syndrome, one finds either reduced activity of the cyclooxygenase or of the thromboxane synthetase. There is no storage-pool defect. The granules are fully present as regards type, number, and contents. The aggregation in response to collagen does not occur or is incomplete. After the addition of ADP or adrenaline to platelet-rich plasma, only the first phase of aggregation is detectable. There is no release reaction in spite of the intact storage organelles. In individual cases with reduced thromboxane synthetase activity complete aggregation can be achieved. So far, we are uncertain as to the causes of the release disorder combined with the impaired prostaglandin metabolism in the platelets.

Clinical Features, Diagnosis, and Treatment. The mode of inheritance has not yet been definitely established. A tendency to bleeding persists life-long, but is however mild. The impairment of platelet aggregation corresponds to that in storage-pool disease, although in addition there is a lack of reaction to arachidonic acid. It is not always possible to draw the distinction on the basis of aggregation inhibition. It is usually necessary to quantify the storage pool contents. In both cases, only the first phase of aggregation occurs in response to ristocetin. The treatment of all of these defects mentioned corresponds to that in "storage-pool" defect.

Acquired Thrombocytophathies

Introduction

Acquired platelet function disorders constitute the largest group. They are produced by drugs and in case of a manifest hemorrhagic diathesis are frequently the consequence of drug combinations whose individual components have various points of attack on the platelets. The platelet defects that can occur during many different diseases are complicated and have not been elucidated in all cases as regards pathogenetic mechanisms. Often, the functional defects are combined with thrombocytopenia and disorders in plasma clotting. The diagnosis of platelet functional disorder is based on the clinical picture, with the typical hemorrhagic symptoms, the drug history, the underlying disease, which is usually accompanied by a platelet disorder indicated by experience, in addition to the results from functional tests, mainly reduced platelet aggregation. In many cases, it is neither possible nor necessary to elucidate the special complex mechanisms in platelet function disorder, particularly since the conditions have multiple causes. The treatment is based on the underlying disease or the causative mechanism, insofar as it is known.

Drugs

A single drug having an effect on platelet function in general produces no manifest hemorrhagic diathesis. A tendency to bleeding can occur

in the simultaneous administration of several drugs with identical or different points of attack on the platelets or if there is simultaneously a hemostasis disorder (hemophilia, liver disease, etc.). Many antiphlogistic drugs and antirheumatics inhibit platelet functions. The best known and most extensively studied is *acetylsalicylic acid.*

The cyclooxygenase in the platelets and megakaryocytes in the bone marrow is acetylated, which inactivates the enzyme and suppresses the production of prostaglandin endoperoxides, as well as the subsequent products, of which the potent proaggregatory factor thromboxane A_2 is clinically of the greatest significance. The bleeding time is prolonged, and the second phase of platelet aggregation following ADP and adrenaline does not occur, while the aggregation induced by collagen is dependent on the dose of acetylsalicylic acid taken and the amount of collagen in the test sample. The release reaction is affected. The acetylation of the cyclooxygenase is irreversible. The inhibition of the enzyme persists throughout the complete platelet lifetime or from seven to 11 days. After a single dose of acetylsalicylic acid, the aggregation ex vivo normalizes in 3–4 days, because the prostaglandin system in the newly produced platelets is not affected and compensates for the defect in the inhibited ones. Shortened platelet lifetimes in various states, e.g., following the implantation of artificial heart valves, is not lengthened by acetylsalicylic acid. Also, acetylsalicylic acid damages the mucosa, with the result that erosions or ulcers can occur in the gastric mucosa, from which there can be clinically relevant bleeding. The daily occult gastrointestinal blood loss following acetylsalicylic acid treatment may be 2–10 ml. Acetylsalicylic acid also inhibits the cyclooxygenase in the vascular wall, with consecutive reduction in the prostacyclin production. It has however not yet been confirmed that there is certainly an unfavorable effect on the balance between thrombocytic and vessel-wall prostaglandin systems with shortening of the bleeding time and the thrombogenic effect after high doses (3 g). The inhibition of the endothelial cyclooxygenase is said to be less than that in the platelets, while the enzyme turnover is said to be higher, so it is assumed that a low dose (50 to 300 mg/day) results in mainly or exclusively the clinically desired inhibition of platelet function. The usual daily dose of acetylsalicylic acid is between 1 and 1.5 g.

Sulfinpyrazone is chemically similar to phenylbutazone. The inhibition of the prostaglandin system is competitive, in contrast to acetylsalicylic acid. The change in platelet function is in principle the same.

The ex vivo effect on platelet aggregation is shorter. The usual dose is 600–800 mg/day. The bleeding time is not lengthened, but there is normalization of the shortened platelet lifetime. It has not been shown that there is measurable intestinal blood loss following sulfinpyrazone.
Phenylbutazone and its derivatives occur in many drugs and drug combinations, and they interfere with platelet function and can give rise to a hemorrhagic diathesis under certain conditions.
The effects of *dipyridamol* on the in vitro function of platelets is not very pronounced. The compound probably inhibits the thrombocytic phosphodiesterase, with consequently reduced destruction of cyclic AMP. Shortened platelet lifetimes, such as in arterial thrombosis and heart valve replacement, may be normalized, particularly in combination with acetylsalicylic acid. No hemorrhagic diathesis arises in the exclusive administration of dipyridamol.
Dextran alone produces no hemorrhagic diathesis. The bleeding time is lengthened, while the platelet aggregation and release reaction are reduced. The peak in the response following dextran infusion occurs at 4–8 h. This appears to be based on a transient refractoriness following intravascular platelet stimulation. Dextran 70 and dextran 40 produce similar effects. On account of the more rapid elimination, the effects of dextran 40 decline earlier.
Heparin can inhibit platelet aggregation and adhesion. High doses can produce a tendency to aggregate or accentuate it if it is induced by other stimulators. A predominantly refractory state is related to the inhibition by heparin, as with dextran, following a precedent activation of the platelets by the heparin.
Penicillins, carbenicillins, and *cephalosporins* inhibit aggregation and release and interfere with platelet adhesion to the subendothelium. A hemorrhagic diathesis can be observed after high doses.
Other compounds with proven effects on platelet function such as theophylline, caffeine, and so on have no clinical relevance.

Other

In *uremia,* one finds clotting disorders and thrombocytopenia. Effects of platelet function appear to be the principal cause for the hemorrhagic picture. The bleeding time is lengthened, while the platelet retention and aggregation can be reduced. Effects on prostaglandin

metabolism have been described. The bleeding tendency usually improves under dialysis.

In *liver diseases,* one can get inhibition of platelet aggregation. This is governed by a platelet defect as yet undefined as well as by the effects of circulating fibrinogen-fibrin cleavage products. A hemorrhagic diathesis is produced by the accompanying thrombocytopenia and the effects on the plasma clotting system in advanced disease.

In *myeloproliferative diseases* (chronic myeloid leukemia, polycythemia vera, thrombocythemia, and osteomyelofibrosis) one gets hemorrhagic symptoms, but also thromboses. These are not necessarily observable. There have been observations on aggregation defects and storage-pool disease. There may also be an influence on prostaglandin metabolism, with reduced production of thromboxane A. Hyperaggregatory states occur. The bleeding tendency mostly improves following myelosuppressive treatment, while the tendency to thrombosis can be treated successfully with platelet aggregation inhibitors. Similar disorders have been described in acute leukemia. The inhibition of adhesion and aggregation and the reduced platelet factor 3 availability in paraproteinemia have been ascribed to a so-called coating effect of the pathological protein on the platelets. The bleeding time is lengthened and can be normalized by plasmapheresis. Laboratory tests indicate a similar platelet function disorder in *glycogen-storage disease* type I (glucose-6-phosphatase deficiency), which is explained by the chronic hypoglycemia and can be rectified by glucose infusion. The platelet function disorder in *vitamin B_{12} deficiency, diabetes,* and *autoimmune diseases* is at present of uncertain etiology. Numerous findings have been reported.

Thrombocytosis and Thrombocythemia

One can distinguish autonomous thrombocytoses and reactive ones. Table 1 gives a survey. A platelet count of more than 400000 to 500000 per mm^3 is pathological. In primary and secondary forms of increased platelet production, values of one to two million per mm^3 may be attained. In primary thrombocytosis, one mainly gets bleeding complications and thromboses (see the preceding section). There is no close correlation with the platelet count in the peripheral blood. Gastrointestinal or mucosal bleeding and epistaxis are common. 20% of the

patients have peptic ulcers. Thromboses occur in the venous system and in the arteries. The mesenteral and spleen veins are mainly affected. Pulmonary embolisms are common. Arterial thrombotic events occur in the form of acral ischemia with gangrene, transitory cerebral attacks, and amaurosis fugax. There is frequently an impaired platelet aggregation in response to adrenaline, whereas the ADP-induced and collagen-induced aggregation is usually normal. Secondary thrombocytosis usually shows no functional defects in the platelets. There is no tendency to bleeding. However, thrombosis is common. Apart from the treatment of the underlying disease, it is particularly indicated to give anticoagulation treatment with heparin and coumarin derivatives as well as platelet clumping inhibitors in secondary thrombocytosis. Anticoagulants are effective, because the coagulation-enhancing effect of the thrombocytes on the plasma clotting system is raised.

VI. Vascular Hemorrhagic Diatheses

Introduction

Vascular-controlled bleeding tendencies can be subdivided into primary congenital and secondary ones, the latter acquired during an underlying disease (Table 3). The bleeding types correspond to those in thrombocytopenia and thrombocytopathies; the bleeding is mainly petechial. Bleeding after trivial injuries, nasal bleeding, bleeding after tooth extraction or operation, and menorrhagia are typical characteristics. The localized vascular malformations lead to circumscribed bleeding in one or more organs, in accordance with the localization of the vascular defect. Such conditions are easy to diagnose if the vascular malformation occurs at an accessible point.

Congenital Vasopathies

Hereditary Hemorrhagic Teleangiectasia (Osler, Weber, and Rendu). This disease was first described by Rendu (1896) and Osler (1901). It is inherited in an autosomal dominant fashion. There is frequently a family history. The bleeding tendency decreases during the course of life. Both sexes are about equally affected. The vascular malformations are circumscribed but multiple. The bleeding is restricted to the sites of the vascular malformations. The vascular lesions consist in widened arterioles and capillaries, with deficiency or defect in the subendothelial elastic tissue. The teleangiectases occur in the skin, subungually, on the lips, in the oral mucosa, on the tongue, on the face, on the hands, in the esophagus and stomach, and less often in the

Table 3. Classification of vascular nonthrombocytopenic hemorrhagic diatheses

Primary disorders
1. Hereditary hemorrhagic teleangiectasia (Osler, Weber and Rendu)
2. Cavernous giant hemangioma (Kasabach-Merritt syndrome)
3. Hereditary connective-tissue diseases
(I) Ehlers-Danlos syndrome
(II) Pseudoxanthoma elasticum
(III) Marfan syndrome
(IV) Osteogenesis imperfecta
4. Albinism
5. Homocystinuria
6. Purpura simplex
7. Senile purpura
Secondary disorders
8. Schoenlein-Henoch purpura
9. Metabolic purpura
(I) Scurvy
(II) Diabetes mellitus
(III) Cushing's syndrome, steroid treatment
(IV) Pernicious anemia
(V) Uremia
(VI) Liver diseases
10. Dysproteinemia
11. Amyloidosis
12. Purpura fulminans
13. Purpura in infectious diseases
14. Embolic purpura
15. Drug-induced vasculitis
16. Purpura following cardiopulmonary bypass
17. Mechanically induced purpura

lungs and urogenital system. The lesions consist of flat round red to violet efflorescences 2–3 mm in diameter, which vanish under pressure. Pulmonary arteriovenous fistulas, which can be multiple, occur in about 20% of patients. Quite frequently, the disease is associated with liver cirrhosis and splenomegaly.

Visible bleeding on the skin or mucosae is readily identified. Diagnostic difficulties occur with organ bleeding, as well as with intestinal or pulmonary hemorrhage. Chronic bleeding can produce hypochromic

anemia. If the course of the disease is uncomplicated, there are no deviations in the clotting system. In up to 50% of patients, there is subthreshold elevated turnover in the clotting factors, which sometimes can go over to acute consumption coagulopathy. The activation of the hemostasis system is a consequence of the altered rheological condition in the diseased areas and the altered vascular surfaces (compare Kasabach-Merritt syndrome).
The bleeding is inhibited by local measures, cauterization of the nasal mucosa being possible. Intestinal bleeding requires operation under certain conditions. Pulmonary hemorrhages represent a difficult therapeutic problem. There may be remission in the bleeding tendency during pregnancy. For this reason, estrogen treatment has been suggested. Substitution is required for iron deficiency.

Cavernous Giant Hemangioma (Kasabach-Merritt syndrome). The syndrome was described by Kasabach and Merritt in 1940. The extensive cavernous hemangioma is a benign tumor of the blood vessels and consists histologically of thin-walled broadened venules. The occurrence is mainly in the skin, but the condition may also occur in internal organs such as the liver and spleen. The changes in the hemostasis system are governed by the elevated turnover in the clotting factors and platelets either in the sense of a latent compensated consumption reaction or as acute consumption coagulopathy with distinct falls in the platelets, fibrinogen, and other clotting factors. In these cases, the hemorrhagic diathesis is generalized. The cause or mechanism for the turnover increase lies in the altered rheological conditions in the hemangioma and in contact activation due to the abnormal endothelium. The treatment consists in excision or irradiation. Consumption reactions can be interrupted with heparin.

The *Ehlers-Danlos syndrome* (Ehlers 1901 and Danlos 1908) is inherited either in autosomal dominant fashion, recessively, or via the X chromosome. It is characterized by hyperelasticity, ease of skin injury, excessive mobility in the joints, and tendency to bleeding. The latter occurs as a consequence of microscopic injuries and is seen as subcutaneous hematomas, purpura, bleeding following tooth extraction, gastrointestinal bleeding and hemoptyses. The disease is due to a deficiency of and defects in the collagen and elastic fibers. The clotting parameters are usually normal, although isolated platelet function disorders have been described.

In *Pseudoxanthoma elasticum,* there is a defect in the elastic fibers. The hemorrhagic diathesis becomes manifest in the second and third decades of life. The disease is inherited as an autosomal recessive one. There are characteristic skin folds on the neck and face, and in the axilla and in the inguinal region. Here one finds teleangiectases. Spontaneous bleeding occurs everywhere on or in the body, but particularly in the skin, eyes, kidneys, joints, uterus, and gastrointestinal tract. The clotting parameters are not altered. Sometimes, there is a tendency to thrombosis.

Marfan's syndrome is characterized by skeletal abnormalities (arachnodactylia), heart defects, vascular defects, lens dislocation, and a hemorrhagic diathesis. The mode of inheritance is autosomal dominant. There is a connective-tissue deficiency involving the collagen and elastic fibers. Bleeding occurs after trivial injury. The tendency to bleeding following injury or operation can be massive. The rest of the clotting status has no special features.

Osteogenesis imperfecta is an autosomal dominant disease. It makes itself felt by deformation and fragility in the bones. There is sometimes a tendency to bleeding. The cause appears to lie in erroneous collagen-fiber synthesis.

In *Albinism,* one can sometimes find a vascular hemorrhagic diathesis. Sometimes, there are platelet function disorders corresponding to the Hermansky-Pudlak syndrome.

Homocystinuria is an inherited disease (autosomal recessive) and is characterized by lensectopy, skeletal abnormalities, and muscular weakness. The fault lies in reduced activity of cystathionine synthetase in the liver, brain, and fibroblasts. Homocystine interferes in the intermolecular cross linking in collagen. There is a tendency to gastrointestinal bleeding, but also to thrombosis.

Purpura simplex occurs in young women. One gets petechiae and minor patches of bleeding without alteration in the skin mainly on the arms and upper leg. Sometimes, the purpura has a familial element. Pathological findings do not occur.

Purpura senilis occurs spontaneously in old people, mainly on the outer sides of the lower arms, the hands, and sometimes the face. The cause lies in vascular wall weakness arising at advanced ages. These two forms of purpura do not require treatment.

Retinocerebellar angiomatosis (von Hippel-Lindau) was first described in 1927. It is characterized by retinal and cerebellar angiomatosis. It resembles Osler's disease, the Kasabach-Merritt syndrome, and the Sturge-Weber syndrome in that hemangiomas can lead to local bleeding on account of rupture and the corresponding clinical symptoms.

Acquired Vasopathies

Allergic Anaphylacatoid Purpura (Schoenlein-Henoch)

Definition, Etiology, and Pathogenesis. Schönlein in 1837 described the disease picture as peliosis rheumatica with joint involvement and purpura. In 1874, Henoch described purpura with accompanying gastrointestinal symptoms. The disease is an allergic vasculitis of various origins. About a third of the patients have elevated antistreptolysin-O titers as a consequence of previous infection with streptococci. Otherwise, the causes have been found in bacterial infections and in foods. One gets perivascular infiltration with neutrophil leukocytes and macrophages.

Clinical Features and Diagnosis. The disease occurs mainly at the younger ages; at 2–3 weeks after the infection, there is a maculopapulous exanthema with urticarial and in part necrotic symptoms and purpura. The preferred sites are the stretching sides of the extremities near the joints, the trunk, and the gluteal area. There is joint involvement in about 60% of patients, abdominal symptoms in 50–80% and kidney involvement in 20–60%. One can also get associated pleuritis, pericarditis, and pneumonia, as well as cerebral purpura. The condition lasts for 4–6 weeks. Persistent glomerulonephritis can make the disease chronic.

Purpura Fulminans

Here the disease picture is different from that in Schönlein-Henoch purpura. Histologically, one finds diffuse extensive hemorrhages in the skin, with consequent necrosis. One can get involvement of the gut, bladder, brain, and serous tissues. There have also been reports of signs of vasculitis with leukocyte infiltration and fibrin necroses in the

small arteries. Capillaries and venules contain thrombi. The disease affects mainly young men. It occurs more frequently following virus infections in the respiratory tract, after varicella, German measles, and scarlet fever. The purpura appears four weeks after the start of the disease. The disease has parallels with the Shwatzman reaction. There are signs of disseminated intravascular clotting. The treatment consists in treating the underlying disease and using heparin to terminate the intravascular clotting activation.

Purpura Following Infectious Diseases and from Other Causes

Purpura can occur following the ingestion of numerous drugs. It is caused then by antigen-antibody reaction with the vascular walls, and by the deposition of immune complexes or by direct injury. Similar mechanisms play a part in purpura consequent on numerous bacterial and viral infections. Sometimes, there is associated thrombocytopenia. The symptoms vanish after the elimination of the drug or improvement of the disease.

There is injury to the terminal vascular system with hemorrhagic diathesis in various metabolic disorders: *vitamin C deficiency, diabetes mellitus, Cushing's syndrome, uremia,* and advanced *liver disease.*

Thrombohemorrhagic symptoms are frequently found in association with diseases involving *paraproteinemia.* In macroglobulinemia, multiple myeloma, cryoglobulinemia, and also amyloidosis, one finds thrombotic processes in addition to bleeding tendencies. These are related to vascular damage and effects on the platelet function due to cell surface coating. The hyperviscosity syndrome is mainly responsible for the tendency to thrombosis. The therapy lies in treating the underlying disease.

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VII. Surgery and Bleeding

Preoperative Diagnosis

Before every surgical operation, coagulation disorders must be excluded, or the hemorrhagic diathesis be diagnosed with reference to type and extent. This is done by consulting the patient's own case history and that of his family, by physical examination and by a preoperative programme of coagulation analysis.

The case history and the physical examination must be carried out carefully (Table 1/III). Mild hemorrhagic diatheses do not necessarily give results deviating from the norm in global and group coagulation analysis tests. Differential diagnosis from the coagulation analysis becomes necessary if there are reports of the occurrence of hematomas after slight injuries, or severe bleeding after tooth extractions, tonsillectomies and other operations. A careful watch must be kept for frequent swelling of joints, hematuria, melena, menorrhagia and prolonged bleeding after births. A drug history is important, with special attention to anticoagulants, antirheumatics and hormone preparations. Many drugs have as a side-effect latent hemorrhagic diatheses, mainly through the effect on thrombocyte function or the strengthening or weakening of an anticoagulant effect. Venous thromboses and pulmonary embolisms suffered in the past are indicators of an increased tendency to coagulate which, apart from protein C and antithrombin III deficiency, is not easy to see or can be seen only vaguely by coagulation analysis. The prophylaxis and treatment of perioperative thromboembolic complications are discussed elsewhere. With the program of coagulation analysis shown in Table 2/III, relevant hemorrhagic diatheses can be recognized and classified. If the case history is

unremarkable, the minimal program of Quick test, partial thromboplastin time, thrombin time, thrombocyte count and bleeding time is sufficient. For minor operations in some circumstances coagulation analysis can be entirely dispensed with. If the result of one or more of the tests is pathological, in some circumstances an analysis of individual factors is necessary to locate the hemostatic disorder exactly and to determine the intensity of the defect.

Preoperative Treatment of Defects of Hemostasis

In *hemophilia A*, after small hematomas and minor injuries, an initial factor VIII level of 5–10% is to be aimed at, and it should be maintained for 2 to 3 days. For minor operations a factor VIII level of at least 10–20% for a week should be aimed at, and should not fall below 5–10% until the wound is completely healed. For major operations, fractures and intracranial bleeding the factor VIII level must be over 50% of the norm for at least 1 week, and must not fall below 20 to 30% until the wound is completely healed. In tooth extraction, if the factor VIII or factor IX activity is above 10% and not more than 1 or 2 teeth are to be extracted, hospitalization is as a rule not necessary, and in some circumstances substitution therapy can be dispensed with. In moderately severe hemophilia with factor activity between 3 and 10%, and severe hemophilia the treatment demands hospital supervision and substitution therapy. The lowest concentration of the factors must be around 20%. If more than one tooth is extracted, a higher concentration of 30–40% is to be aimed at. The duration of the substitution therapy extends to 2 to 5 days, and in severe hemophilia up to 10 days after the tooth extraction. An antifibrinolytic, epsilon-aminocaproic acid 1 g/10 kg or AMCHA 0.1 g/10 kg body weight per day may reduce the danger of bleeding. The foregoing notes apply also to the procedure in the case of *hemophilia B*.
Substitution in hemophilia A is carried out with purified factor VIII preparations, and in hemophilia B with factor IX concentrates or prothrombin complex preparations. Tables 3/IV and 4/IV give a summary of the factor level and duration of substitution. Owing to the shorter half-life, half the initial dose is to be given every 6 to 8 hours in hemophilia A, and in haemophilia B 12-hourly substitution is sufficient. Where there are antibodies against factor VIII the preparations

FEIBA (Immuno) or Autoplex (Travenol) are used. With a titer of inhibitor of under 5 Bethesda units/ml, the inhibitor can be overcome with factor VIII concentrates. When substitution is continued a watch must be kept for later increases in the inhibitor. In individual cases where there is a high inhibitor titer, plasmapheresis can be considered.
In *dysfibrinogenemia, hypofibrinogenemia and afibrinogenemia,* 2 to 5 g of fibrinogen preoperatively is sufficient. The maintenance treatment until the wound has healed consists of 1 to 5 g of fibrinogen every 2 to 3 days. A minimal concentration of 100 mg% of fibrinogen is to be aimed at. In dysfibrinogenemia a functional test should be used to determine the fibrinogen.
In congenital *factor XIII deficiency* a concentration of 3 to 10% of the norm is sufficient for hemostasis. Higher factor XIII levels should be obtained if the wound is to heal without complications. The preoperative substitution therapy of 2500 units of factor XIII concentrate (Fibrogammin, Behringwerke) is recommended, and for 5 days after the operation or until the wound has healed 500 to 1000 units every day or every 2 days.
In congenital *deficiency of factors V, XI, XII,* and in *von Willebrand-Jürgens syndrome,* substitution is carried out with fresh plasma or fresh-frozen plasma, antihemophilic globulin or cryoprecipitate. The initial dose is calculated as for factor VIII deficiency. The intervals for the maintenance dose are according to the half-life of the individual factors.
In *deficiency of factors II, VII and X* prothrombin complex preparations are used as for hemophilia B. The maintenance dose is similarly based on the half-life of the factors. Factor VII has the shortest half-life, 5 to 6 hours.
In *parenchymatous liver damage* vitamin K may be tried. Success is as a rule only moderate. If the Quick value is under 30%, the substitution of prothrombin complex preparations is necessary, depending on the intervention planned. The dose is calculated as for hemophilia B. Substitution of antithrombin III, fibrinogen and thrombocytes is necessary in individual cases.
The frequency of substitution in all the foregoing hemostatic disorders is influenced by the severity of the operation trauma and the perioperative progress with possible circulatory insufficiency etc.; in short, conditions which raise the metabolism of the coagulation factors used.

In patients who have had anticoagulation therapy with *coumarin derivatives*, minor operations and tooth extractions can be carried out if the thromboplastin time is only a little below the therapeutic limit, or the Thrombo-test shows 20%, and the Quick value and Hepato-Quick show 30%. In moderate operations and arteriography the Quick value should be over 40%. This is obtained by a pause in treatment of 3 to 6 days. The waiting time can be shortened by giving 3 to 5 mg of vitamin K orally. After 24 hours the Quick value is approximately within the desired limits. Major operations need a Quick value of above 50 to above 60%. Anticoagulation must be discontinued about 6 days before the operation. 5 to 10 mg of vitamin K shortens the waiting time to about 2 days. For urgent operations the factors of the prothrombin complex II, VII, IX and X reduced can be immediately normalized by coumarins by prothrombin complex preparations. Perioperative maintenance substitution is necessary, calculated in the same way as for hemophilia B, until the liver has built up the factors of the prothrombin complex in sufficient amounts. The short life of factor VII should be taken into account. Table 2/XIV gives an indication of the procedure to be used.

Difficulties arise when an operation is needed by a patient with *consumption coagulopathy with or without fibrinolysis*. If the cause or partial cause of the comsumption reaction is removed, e.g. a hypovolemic traumatic shock, as far as it is possible from the surgical point of view, the operation should wait until hemostasis has been recompensated. The disturbance of hemostasis either disappears spontaneously or can be removed by substitution of fresh plasma or fresh-frozen plasma, with heparinization at the same time if necessary. If consumption coagulopathy is further maintained by, for example, an infected abortion, a retroplacental hematoma, a retained fetus, injured tissues and a focus of sepsis in any location, and cannot be influenced, an operation is necessary to remove the cause. The operation must be completed as quickly as possible. After that the coagulation disorder disappears as a rule. Especially in the case of sepsis perioperative heparinization is to be recommended in a dosage of about 15000 IU per day or an initial dose of 2000–3500 IU followed by 500–700 IU per hour. If the hemostasis potential is exhausted, the preoperative use of fresh plasma, fresh-frozen plasma, if necessary fibrinogen, cryoprecipitate and prothrombin complex preparations is required. Factor concentrates should always be given under heparin

protection, as they contain, to a varying extent, activated coagulation factors, which may accentuate the consumption reaction. In cases of thrombocytopenia and thrombocytopathies, according to the extent of the hemorrhagic diathesis, fresh blood, platelet-rich plasma or thrombocyte concentrate, and if necessary also fresh plasma should be given. One unit of fresh blood (450 ml) contains about 1.0×10^{11} thrombocytes. One unit of platelet-rich plasma (220 ml) contains $0.7–0.9\times10^{11}$ thrombocytes. Thrombocyte concentrate contains 0.5 to 0.7×10^{11} thrombocytes in 20 to 50 ml. By cell separation between 2 and 9×10^{11} thrombocytes can be isolated from a single donor. For one substitution, 4 to 8 units are necessary. As thrombocytes do not keep well, the transfusion must take place 4 to 6 hours after the preparation is made. Further substitution at intervals of about 2 days is determined by the success of the treatment in removing the hemorrhagic diathesis, by the bleeding time and by the thrombocyte count.

Perioperative Bleeding

If bleeding is acute it must be decided whether it has an exclusively local cause, or whether the extent of the bleeding is out of proportion to the local situation. In the latter case we must consider first of all consumption coagulopathy, hemophilia A, von Willebrand-Jürgens syndrome and thrombocytopenia of whatever origin. The remaining hemorrhagic diatheses are rare. Until the hemorrhagic diatheses assumed to exist are elucidated by the case history and by coagulation analysis, fresh blood, fresh plasma or fresh-frozen plasma are substituted, and in the second place fibrinogen preparations, Cohn fraction I and cryoprecipitate. Modifications in the coagulation-specific treatment, as in the situations described below, depend on the detailed findings.

If bleeding occurs early in the operation, we must first consider thrombocytopenia and thrombocytopathy (von Willibrand-Jürgens syndrome). We may also consider subhemophilia, unsuspected until now. First the bleeding time and thrombocyte count must be determined. An acute minimal program of coagulation analysis must be started at once. Bleeding occurring in the further course of the operation has mainly surgical causes. Mild hemophilia is possible, as also are congenital hermorrhagic diatheses of various origins, or anticoagulant treat-

ment of the patient with coumarin derivatives unknown to the surgeon.

If bleeding occurs in the later intraoperative phases, besides the causes already mentioned, it is most likely to be the result of consumption coagulopathy with or without secondary fibrinogenolysis, and in rare cases primary fibrinogenolysis. Besides the bleeding at the site of the operation, the hemorrhagic diathesis shows itself through generalized bleeding of the plasmatic and thrombocytic type, typical of the consumption reaction, from the skin and mucous membranes. This happens mainly in operations of long duration, or operations on organs which are particularly rich in activators of coagulation and fibrinolysis. The following situations are particularly prone to cause an intraoperative consumption reaction: serious accidents with shock, tissue hypoxia, acidosis, operations on the prostate, lungs and pancreas, operations of long duration with extracorporeal circulation, operations on patients with cirrhosis of the liver, and liver transplants. We can also expect an increase in turnover in special gynecological operations (premature apruptio of the placenta, septic abortion, amniotic fluid embolism), in massive transfusions and transfusions with incompatible blood. It goes without saying that the hemorrhagic diathesis must be identified immediately by coagulation analysis. Even before the results of the coagulation analysis are to hand, effective treatment can be carried out to some extent. In cases of shock and trauma we have mainly to expect a consumption reaction. As far as the operation situation permits, heparinization with initially 1000–2500 IU is begun, and continued with 250–500 IU per hour. In large-volume substitutions with stored blood and plasma expanders we can expect, besides activation of the coagulation, a so-called dilution or washing out effect of coagulation factors and thrombocytes.The decisive measure is the substitution of fresh blood and fresh plasma. After 4 to 6 full blood infusions the injection of 20 ml of 20% calcium gluconate is to be recommended. In operations on prostate, lungs and pancreas we have to be prepared for a fibrinolysis or finbrinogenolysis. Initially 200,000 to 500,000 KIU of Trasylol and then 50,000 to 100,000 KIU per hour is given. An additional fibrinogen substitution after interrupting the lysis, in a dose of 2 to 6 gr is, besides fresh plasma, the appropriate measure. Epsilon-aminocaproic acid and analogous preparations are to be used with great caution. In urological operations and in proved hyperfibrinogenolysis a dose of 4 to 6 g of epsilon-aminocaproic acid

every 8 hours or 0.5 to 1 g of AMCHA at the same intervals is justified. In unexpected *postoperative bleeding* a surgical cause must first be excluded. We must also consider the possibility of a consumption reaction running a protracted course after circulatory shock taking place during or after the operation, or, in operations with extracorporal circulation, incomplete heparin neutralization, or renewed release of heparin which occurs mainly through neutralization with protamine sulfate, and less often through protamine chloride, or overdosage with protamine. Further we have to consider an overdose of anticoagulants in perioperative thrombosis prophylaxis; if the bleeding begins 1 to 2 days after the operation there may be mild hemophilia in which the primary hemostasis was without complications, or there may be a factor XIII deficiency. There is as a rule enough time for a coagulation analysis. The treatment is then decided according to the results, and is discussed elsewhere.

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B. Thromboembolic Diseases of the Venous and Arterial Vascular Systems

Indications for Treatment with Antithrombotics and Fibrinolytics – A Review

In Table 1 diseases and conditions are tabulated in which treatment with anticoagulant drugs or fibrinolytics are indicated. It is only intended to give here a review of the possible scope of indications in cases in internal medicine and surgery. The majority of diseases are fully discussed elsewhere. The sections relating thereto are quoted. Where in the Table several drugs are mentioned, we are dealing with alternatives which are used depending on the actual situation and the aim of therapy, or else different phases in the course of diseases in which a modification of the coagulation controlling therapy may appear of value. The Table contains both absolute and also relative indications for a coagulation-specific therapy. The former is un-

Table 1. Indications for antithrombotics and fibrinolytics

	Heparin	Oral anti-coagulants	Thrombo-cyte-aggregation inhibitor	Fibrino-lysis
+ Venous thrombosis				
Treatment	●	○		●
Prophylaxis	●	●		
+ pulmonary embolism	●	○		●
Cor pulmonale	●	●		○

Table 1. (Continued)

	Heparin	Oral anti-coagulants	Thrombo-cyte-aggregation inhibitor	Fibrino-lysis
+ Myocardial infarction				
acute	●			○
hospital phase	●	●		
secondary phase		●	●	
Coronary heart disease		●	○	
Angina pectoris				
Cardiomyopathy		●		
Heart failure		●		
+ Heart valve replacement		●	○	
Aortocoronary bypass		●	●	
+ Atrial fibrillation		●		
Embolic disease				
Peripheral arterial embolism	○	●		
Cerebral embolism	○	●		
Transitory ischemic attacks		●	●	
Peripheral arterial occlusive disease after		●	●	○
Thromboendarteriectomy		○	●	
after bypass operation		●	○	
+ Hemodialysis	●			
Arteriovenous shunt		●	●	○
Hypercoagulability	●	●		
Elevated coagulation potential				
Polycythemia		●		
Thrombocytosis		●	●	
Hyperfibrinogenemia		●		
Antithrombin III deficiency		●		
Tumor irradiation		●		
Pelvis, Thorax				
Circulatory shock	●			
"low flow state"				
Consumption coagulopathy	●			○

+ = absolute indication, ○ = rare complementary special alternative indication, ● indication

equivocally established on the basis of many years experience and of studies of the prophylactic and therapeutic effects. In the latter case a positive effect of the therapy can be assumed on the grounds of clinical experience and of the basic pathogenetic mechanisms, and often can be considered as certain. The decision on treatment is made in each case depending on the individual patient and the danger of thrombosis which exists. This is always assumed when the disease is accompanied by heart failure with reduced cardiac output and conditions in which an increased coagulability and an elevated coagulation potential of the blood exist (Table 3).

In the acute phase of a venous thrombosis heparin and fibrinolytics are indicated. Oral anticoagulants are introduced in the after-treatment phase to avoid a recurrence. The same is true for pulmonary embolism. The duration of the oral anticoagulant therapy in uncomplicated venous thrombosis extends to 3–6 months, that of uncomplicated lung embolism to 6–12 months. In recurrence under certain circumstances it is to be carried out life-long. The prophylaxis of deep venous thrombosis is carried out in hospital with subcutaneous "low dose" heparin treatment, which is also carried out on ambulant patients. As a rule ambulant prophylaxis consists of administration of oral anticoagulants. With a mesenteric, portal vein or splenic vein thrombosis fibrinolysis treatment is only exceptionally indicated due to the danger of hemorrhagic infarction. Long-term anticoagulation is sensible in the chronic stage. Cor pulmonale requires anticoagulation when right heart failure or polycythemia exists, and in any case, when a cor pulmonale vasculare is present, especially as a consequence of recurrent microemboli. In the last case fibrinolytic treatment can be indicated, which, if carried out early, can decrease the pulmonary arterial pressure. With reference to cardiac infarction, the appropriate chapter should be consulted. In coronary heart disease and stable and unstable angina pectoris accompanying thrombotic processes are assumed. For prevention of progressive vascular disease and coronary thrombotic events the oral anticoagulants have hitherto been predominantly used. With the conception of the participation of thrombocytes on the progression of coronary stenosis, and of the occurence of rhythm disorders through microemboli in the periphery of the coronary vascular system, aggregation inhibitors have been increasingly used in prophylaxis and therapy. In cardiomyopathy and heart failure, treatment with oral anticoagulants for the prevention of deep leg vein

thrombosis and thrombus formation in the heart cavity is carried out at least until cardiac recompensation occurs. After heart valve replacement, thrombocyte aggregation inhibitors together with anticoagulants are used in special cases only. The positive effect of coagulation inhibiting therapy after aortocoronary bypass is still subject to discussion. In atrial fibrillation, especially in mitral stenosis and dilatation of the left atrium, anticoagulation is indicated for the inhibition of atrial thrombi and consecutive peripheral embolism. In these cases an anticoagulation is also justified after a cerebral embolism for recurrence prophylaxis. In transitory ischemic attacks and conditions after vascular operations numerous studies have been carried out which illustrate the positive effects of anticoagulant therapy.

The progression of peripheral arterial occlusive disease is probably halted by oral anticoagulants. No satisfactory investigations have been carried out on the value of aggregation inhibitors. The fibrinolysis therapy of arterial occlusive disease is reserved for special indications, which are dealt with in the corresponding section. Anticoagulation is a self-evident requirement during hemodialysis and hemoperfusion. Recently increasing reports have appeared which state that through the infusion of prostacyclin, heparinization can be reduced, or even in individual cases made superfluous. Despite the uremic bleeding tendency, the prophylaxis of re-occlusion with oral anticoagulants or aggregation inhibitors can be indicated in recurrent shunt thrombosis. In many cases a hemodialysis shunt with a recent occlusion can be reopened by local fibrinolysis treatment with relatively small amounts of streptokinase or urokinase, which are without systemic action. In all diseases which are accompanied by hypercoagulability or an increased coagulation potential, thrombosis prophylaxis is usually sensible. It is usually carried out with oral anticoagulants, but with reliable patients or in the ward it can also be carried out over a longer time by the subcutaneous route. Circulatory shock and consumption coagulopathy are indications for heparin therapy, for the avoidance of deep pelvic-leg vein thrombosis and fibrin deposition in the microcirculation. In consumption coagulopathy, with assumed fibrination of the vascular periphery, fibrinolysis treatment is indicated despite the existing hemostasic defect.

VIII. Venous Thrombosis and Pulmonary Embolism

Venous Thrombosis

Frequency of Venous Thrombosis and Pulmonary Embolism

The data on the frequency of venous thrombosis and pulmonary embolism in inpatient material varies depending on the quality and extent of diagnostic measures available. On the basis of clinical investigation results the frequency of thrombosis in patients treated as inpatients, is quoted as up to 5%, pulmonary embolism between 1 and 2%, and the mortality after pulmonary embolism between 0.1 and 1%. In unselected post mortem material venous thromboses are quoted as 1.4–30%. In internal medicine post mortem material, 40–60% of venous thromboses were determined. In 15–20% of these patients with thromboses a pulmonary embolism was demonstrable. Again, of these only 11–15% had been diagnosed clinically, and were regarded as the cause of death in 3–8%. The accuracy of diagnosis of thrombosis and pulmonary embolism without technical equipment is in the most favorable case established as between 50 and 60%. However, it is usually lower (Fig. 1). Since phlebography, the ultrasound Doppler probe, and the radio-fibrinogen test were introduced, it has become clear that without prophylaxis thrombosis occurs in a considerably higher percentage of cases than formerly assumed (Table 2). About 90% of all clinically relevant thromboses occur in the venous region of the lower extremities and pelvis; 4% affect the upper limbs, and 2–4% affect the venous flow regions of other organs. Embolism of all grades of severity occurs with thromboses of the iliofemoral region in about 40% of cases, and in the lower leg in 11–30%.

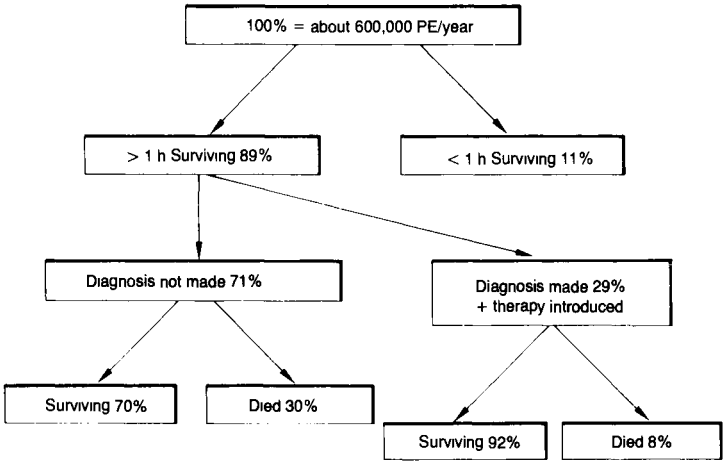

Fig. 1. Frequency, diagnosis, and therapeutic consequences of pulmonary embolism (PE) in the USA (Schöndorf 1982)

Table 2. Frequency of deep vein thrombosis. Diagnostic procedure – Positive radiofibrinogen test (Gallus, Hirsh, 1976)

Operations	
Abdomen	14–33%
Thorax	26–65%
Gynecology	14–19%
Total prostatectomy	24–51%
Transurethral prostatectomy	7–10%
Hip joint prosthesis	48–54%
Fractured neck of femur	48–74%
Puerperium	3%
Internal Medicine	
Myocardial infarction	23–38%
Apoplexy	60%

In the course of months and years complete spontaneous recanalization the deep leg vein thromboses occurs in 35%, and partial recanalisation in 55%. Nevertheless the venous valvular apparatus is extensively destroyed. After heparin therapy a post-thrombotic syndrome develops in 70% in the course of years. Pathogenetic factors (Table 3)

Table 3. Thrombosis promoting factors (Heinrich, Klink 1981)

A. *Stasis*
   a) *Systemically conditioned*
      Immobilization (sedentary activity, confinement to bed, fractures, plaster bandage, paresis)
      Overweight
      Pregnancy, puerperium
      Chronic heart failure
      Chronic lung disease
   b) *Locally conditioned*
      Varicosities
      Postthrombotic syndrome
      Compression (lymphoma, hematoma, abdominal tumors, neuromuscular shoulder-girdle syndrome)

B. *Vein wall lesions*
      Trauma (operative or accidental)
      Hypoxia (acidosis)
      Endotoxins
      Phlebitis
      Degenerative changes (diabetes mellitus)
      Phlebosclerosis

C. *Changes of the coagulation status*
   a) *elevation of procoagulatory factors*
      Thromboplastin overflow (after operative interventions, in metastasizing tumors – especially pancreas, colon, stomach, urogenital tract, lung –, after burning)
      Thrombocytosis (after removal of spleen, in polycythemia vera)
      Hyperfibrinogenemia (metastasizing tumors, infections)
   b) *Lowering of inhibitory factor concentration*
      Fibrinolysis inhibition (diabetes mellitus, hyperlipidemia, corticosteroid therapy, oral contraceptives)
      Antithrombin III deficiency (congenital, acquired in liver insufficiency and pancreatitis)
      Protein C deficiency
   c) *Hyperviscosity*
      Hematocrit elevation (exsiccosis, polycythemia, diuretic therapy)
      Paraproteinemia
      Dysproteinemia
      Cryoglobulinemia

which can occur as accompanying manifestations of a basic disease or as consequences of operative intervention, are hypercoagulability of the blood, hypocirculation, hypofibrinolysis, and hyperviscosity, with or without hyperfibrinogenemia, hyperaggregability of the thrombocytes and thrombocytosis. As riskfactors, advanced age, varicosis, a condition after a previous venous thrombosis, an infection, adiposity, malignancy, paresis, heart failure, an operative intervention, of type and duration over 30 minutes, and operative blood loss, come into consideration. (Beneke, 1980; Heene et al. 1977; Heene, Lasch, 1982; Schmutzler, R., 1981 a)

Clinical Features and Diagnosis of Venous Thrombosis

In the initial phase of occurrence, a thrombosis is clinically scarcely detectable. The symptomatology is uncharacteristic. Leg edema and livid staining of the skin first occur when the thrombus has reached a certain extent, and through appositional growth increasing collaterals are shut off. Frequently the thrombus first becomes clinically apparent 2–4 days after its occurrence. 80–90% of the leg vein thromboses take their starting point in the lower leg. Operations in the hip-joint – thigh region form the exception. Here the thrombus begins in the femoral vein of the limb operated on. About 80% of thromboses are restricted to the lower limb. Of these ⅓ break down spontaneously again. 6–20% of thromboses progress proximally and are potential starting points of hemodynamically active pulmonary emboli. With phlebography the reproducibility and the certainty of demonstration of thromboses for the pelvic veins amounts to 79%, for the popliteal vein and the femoral vein to 95%, and for the veins of the lower leg to 84%. As compared with phlebography, with the Doppler ultrasound probe thromboses in the pelvic region can be diagnosed in 90%, in the thigh region in 76%, in the popliteal region in 67%, and in the lower leg region in 52%. False positives occur in 12% of the investigations.

Whereas the Doppler ultrasound probe is only conditionally usable in the lower leg region, usually requiring control by phlebography, the iodine^{-131} fibrinogen test here agreed with phlebography in 78–97% of cases. Thromboses in the popliteal region are demonstrable with it in 50% of cases, in the thigh region in 30%. For the detection of pelvic

vein thromboses the radiofibrinogen test is not suitable. In particular, after operations in the thigh-hip joint region one obtains no statement on the proximal extent of a thrombosis with the radiofibrinogen test (Heene, Lasch 1982)

Prophylaxis of Venous Thrombosis

The object of thromboembolismprophylaxis is the avoidance of venous thrombosis, fatal and nonfatal pulmonary embolism and the post-thrombotic syndrome. Numerous investigations have been carried out with heparin in various doses and modes of application, with coumarin, dextran and aggregationinhibitors. Systematic studies on the value of physical measures do not exist, or have been carried out only on small numbers of patients. One has to decide between a general prophylaxis and a targetted prophylaxis with endangered patients and specific operations with increased risk of thrombosis. In the minor and intermediate operations on patients up to 30 years old a general prophylaxis can be waived. In persons over 40 years old and extensive operations a general prophylaxis is advisable. In internal medicine it is limited to patients with an increased risk of thrombosis.

Heparin

The impetus for the prophylaxis of venous thrombosis and pulmonary embolism goes back to the investigations of Lenggenager (1957) and Sharnoff (1966). If heparin is given before the thrombogenic stimulus (e.g. operation) relatively small amounts suffice in order to inhibit activated Factor X. The formation of thrombin is inhibited, and transformation of fibrin into fibrinogen does not ensue. If because of the intensity of the thrombogenic events the inhibition of factor Xa is not sufficient, or if heparin was first given after the activation of the coagulation system, higher doses are necessary for the inhibition of the thrombin action. Thus it was shown that "low dose" heparin prophylaxis was less successful after fractures of the neck of the femur in comparison to elective hip joint operations. With the first-mentioned patients activation of the coagulation system with thrombin formation occurs before heparin administration.

"Low dose" heparin prophylaxis means administration of 5,000 I.U. heparin subcutaneously 2–3 times a day. In surgical patients the first heparin administration is started 2 or 4 hours preoperatively. Then follows the administration of the same dose at 8- or 12-hourly intervals during the first 7 postoperative days, or until full mobilization of the patient. About 50% of leg vein thromboses occur intraoperatively; of the remaining 50% the majority occur within the first 3 days after operation. Patients with increased thrombosis risk and the danger of thrombosis occurring in the postoperative course, and also in heart and vascular surgery patients in which a long-term anticoagulation is necessary, are transferred to anticoagulation with coumarin derivatives between the 3rd and 6th postoperative day. Heparin is withdrawn as soon as the thromboplastin time (Quick value, Hepato-Quick, Thrombotest) lies within the therapeutic range. With regard to the reduction of operativelyinduced venous thrombosis, no distinct difference between the daily administration of 3×5,000 I.U. heparin and 2×5,000 I.U. heparin was established. In patients with a high risk of thrombosis the triple administration is nevertheless advisable. A coagulation-analytical control of heparin action by means of the thrombin time or the activated partial thromboplastin time, or a monitoring of the heparin level by means of a chromogenic substrate is as a rule superfluous. A heparin effect or a measurable heparin level is not detectable in the plasma, or only detectable in the first 4 hours after injection. In individual cases with long-acting "low-dose" heparin prophylaxis which extends over more than 5–7 days, an accumulation of heparin with then a clearly prolonged coagulation time can occur. For this reason, expecially with hemorrhagic complications, an occasional monitoring of the thrombin time or the heparin level is sensible. Dihydergotamine increases the venous return. In the hope of being able still further to decrease the frequency of thrombosis, prophylactic schemata have been proposed in which 2 or 3×5,000 I.U. heparin were always administered together with 0.5 mg dihydergotamine. In some studies with dihydergotamine the heparin dose was reduced to 2–3×2,500 I.U. per day. It appears that the additional administration can still further decrease the thrombosis risk. At least the daily administration of 2×5,000 I.U. heparin with 0.5 mg dihydergotamine at the same time seems to be equivalent to the effect of 3×5,000 I.U. heparin. In patients with high risk of thrombosis increasing the dose on the 2nd or 3rd post-operative day to 3×7,500 I.U. is to be considered.

Table 4. Reduction of incidence of fatal postoperative pulmonary embolism by treatment with "low-dose" heparin (Matt, Gruber, 1977)

Authors	No. of patients investigated		Fatal pulmonary embolism		Significance
	Controls	Heparin	Controls	Heparin	
Gruber et al.	1631	1610	18 (1.1%)	6 (0.4%)	$p < 0.05$
Kakkar et al.	2076	2045	16 (0.8%)	2 (0.09%)	$p < 0.005$
Sagar et al.	236	264	8 (3.4%)	0 (0.0%)	$p < 0.01$
Total	3943	3919	42 (0.8%)	8 (0.2%)	$p < 0.001$

Under the thrice-daily administration of heparin, with a similar incidence of thrombosis as after the twice-daily injection, the proximal extension of thrombosis in the popliteal vein, femoral and iliac veins could be decreased from 6% in the control group to 0.6%. This is of especial significance in relation to the inhibition of pulmonary embolisation, which could in this way be significantly decreased. Postoperative blood loss by bleeding complications were significantly more frequent under heparin prophylaxis. Under sodium heparin as compared to calcium heparin the blood loss is said to be somewhat higher, and small hematomas at the injection site are said to be more frequent. The percentage frequency of fatal pulmonary embolisms could be decreased with various doses of "low dose" heparin from 0.8% to 3.4% to 0 to 0.4% of patients (Table 4).

In *general surgery* the mean thrombosis frequency is 35.4%. It varies according to the operation undertaken between 20 and 65%. Under the influence of 3×5,000 I. U. heparin the postoperative frequency of thrombosis of about 66% could be decreased by about one third, under 2×5,000 I. U. heparin per day to about 50% in the mean.

In *orthopedics* with elective hip joint replacement the mean thrombosis frequency amounts to 57.3%. In 90% of patients the extremity operated on is affected, and the femoral vein is affected simultaneously in up to 60% of cases. The relatively high age of the patients, local circulatory disorders of the veins in the operative field, with dilatation of the proximal femoral vein, extensive tissue trauma, and a pronounced postoperative slowing of the blood flow are held responsible for the frequency of the thrombosis. Under treatment with

Table 5. Frequency of deep vein thrombosis (DVT) after elective hip-joint operations and different modifications of heparin prophylaxis. ASL = Acetyllysine (Schöndorf, 1978)

Daily dose	Controls	Heparin s.c.		
		3×5,000 I.U.	3×5,000 I.U. ASL	3×5,000 I.U. 3×7,500 I.U.
No. of patients	15	30	30	38
Patients with DVT	9 (60%)	10 (33%)	8 (27%)	4 (11%)
Bilateral DVT	3 (20%)	4 (13%)	3 (10%)	0
DVT/popliteal-femoral veins	6 (40%)	5 (17%)	3 (10%)	1 (2.6%)

3×5,000 I.U. heparin per 24 hours the thrombosis frequency could be decreased to a mean figure of 20%, and even to 14% according to the compilations of other authors. Because numerous thromboses can still develop between the 7th and the 14th postoperative day, an extension of heparin prophylaxis beyond the 7th postoperative day is advisable. Through combination with dihydroergotamine the frequency of thrombosis can be further decreased. By elevation of the heparin dose to 3×7,500 I.U. per 24 hours the thrombosis frequency can be decreased to 11% (Table 5).

In *gynecology* the mean thrombosis frequency determined by the radiofibrinogen test is 23.8%. It can sink through 2×5,000 I.U. heparin per 24 h. to a mean frequency of 4.6 to 12%. A double heparin administration should be sufficient. If necessary the prophylactic effect can be increased through the additional administration of dihydroergotamine.

The frequency of deep pelvic vein thromboses in *pregnancy* is assumed to be 0.1–0.3%. In this case, the diagnosis has not as a rule been made by objective methods. In the last third of pregnancy the tendency to thrombosis is at its strongest, and is again increased by the existence of risk factors, in particular in conditions arising after a foregoing venous thrombosis. A prophylaxis with 2×7,500 I.U. heparin s.c. is indicated. Heparin does not pass the placental barrier and therefore causes no additional hemostatic defect in the fetus. After several months of heparin administration osteoporosis can occur.

Coumarin derivatives are transferred into the circulation of the child, and produce a hemorrhagic diathesis, which in particular during parturition can lead to cerebral hemorrhages. In about 5% a so-called warfarin embryopathy occurs under coumarin therapy. The period of particular sensitivity lies between the 6th and 8th week of pregnancy. It is characterized in the fetus by hypoplasia of the nose, skeletal changes and airway obstruction as a consequence of maldevelopment of the bronchial cartilage. Cerebral damage, which is probably conditioned by hemorrhage, occurs in 2% of the newborn of mothers who have received coumarin derivatives during pregnancy.

If a fresh thrombosis occurs during pregnancy, first an 8–10 day intravenous therapy with 20–30,000 I.U. heparin, depending on the thrombin time, is carried out. The therapy is continued with 2–3× 7,500 I.U. heparin subcutaneously. With thromboses occurring early in pregnancy it was recommended to give heparin in the first trimester, and after that to change over to coumarin derivates, and in the last 2 weeks of pregnancy to administer heparin once more.

If patients with artificial heart valves are pregnant one is forced to use anticoagulants during the whole pregnancy, either with 3×7,500 I.U. heparin subcutaneous or as indicated above in intervals with coumarin derivatives.

In the *urological patients* the perioperative thrombosis frequency after transurethral prostatectomy lies between 7 and 10%. After retropubic transvesical prostatectomy it occurs in about 50% of cases. Prophylaxis with heparin seems not to decrease the thrombosis frequency in transurethral resection, whilst with the other named operative procedures, the occurrence of thromboses can be reduced to 24% under an 8 or 12 hour administration of 5,000 I.U. heparin.

Neurological patients after stroke attacks and other diseases which are associated with paresis are especially endangered by thrombosis. In about 90% of cases the thrombosis occurs in the paretic extremity. In recent ischemic cerebrovascular insults the frequency of thrombosis could be significantly reduced from 56.1 to 27.5% by the daily administration of 2×5,000 I.U. heparin and 0.5 mg dihydergotamine. The danger of intracerebral hemorrhage as a consequence of heparin therapy is especially high after apoplexy. However, the research workers did not quote a difference from the control group.

From the field of *internal medicine* only a few systematic investigations are available. Thromboses occur in a mean of 35.5% of patients.

After myocardial infarction the frequency of thrombosis decreased from 24 to 5% under the effect of 2×5,000 I. U. heparin subcutaneously. A prophylaxis with 2 or 3×5,000 I. U. should be administered on a large scale. The prophylaxis is indicated in older patients, patients confined to bed for long periods with carcinomas, polycythemias, thrombocytosis and heart failure, especially in the phase of edema mobilization. In patients with congenital or acquired antithrombin III deficiency the additional administration of 1,500–2,000 units of antithrombin III 2× per week should be considered. More appropriate here is anticoagulation with coumarin derivatives. With an antithrombin III level of under 70% of the normal the thrombosis risk is clearly elevated. In liver cirrhosis, besides a reduced formation of coagulation factors, a latent increased turnover of the factors of the hemostasis system can exist, which is associated with a tendency to thrombosis.
The increased turnover is frequently not demonstrable with certainty by coagulation analysis. For the prophylaxis of thrombosis the administration of 2×5,000 I. U. heparin is to be considered. Under some circumstances a hemorrhagic diathesis as a consequence of a consumption of coagulation factors can be favorably influenced by heparin, by a recompensation of the hemostasis system (Czechanowski, Heinrich, 1981; Kakkar 1981a; Marx, Wuppermann, 1981; Matt, Gruber 1977; Schmutzler 1981a; Schöndorf 1978; Schöndorf 1981)

Low Molecular Weight Heparin

The possible advantage of low molecular weight (LMW) heparins by comparison with unfractionated (UF) heparin is considered to be a possibly greater antithrombotic action with less of an anticoagulatory effect and a reduced risk of hemorrhage. It is not yet certain whether these assumptions will be confirmed. The investigations and studies on the dosage, success rate and frequency of bleeding and side-effects have not yet been completed. The longer half-life, which means that only one subcutaneous injection is required daily for prophylaxis against thrombosis, and the absence of any action on the thrombocytes might be an advantage. In rare cases UF-heparins induce a thrombopenia. The fact that treatment surveillance is more difficult and the

only partial inactivation through protamine with the usual dosage may be disadvantageous.

Studies on perioperative prophylaxis against thrombosis comprise 100 to 400 patients in each case. In *general surgery* the subcutaneous dose of LMW-heparin given lies at 1×2,500 and 1×5,000 I.U. anti Xa per day and at 1×1,500, 1×1,850 I.U. aPTT (plus 0.5 mg dihydergotamine (DHE) in each case) and 2×2,400 I.U. anti aPTT. This was compared with 2×5,000 I.U. UF-heparin. The prophylaxis commenced with the first injection 2 hours before the operation and was carried out for 5 to 10 days. With the dose used and the differing administration frequency, there did not seem to be any difference between UF and LMW heparins in respect of the postoperative incidence of thrombosis (radiofibrinogentest). This lay between 3% and 10%. Hemorrhagic complications occurred with equal frequency and lay between 4% and 15%. The frequency of bleeding was distinctly increased with a dose of 7,500 I.U. anti Xa subcutaneously per day.

In *accident surgery* and *elective hip joint replacement* to date 1×5,000 I.U. anti Xa and 1×1,500 I.U. aPTT plus 0.5 mg DHE have been given and compared with 2×5,000 I.U. UF heparin plus DHE. The prophylaxis similarly commenced two hours preoperatively and was continued for 7 days. In respect of the incidence of thrombosis (radiofibrinogen test) there was no difference from UF-heparin at 12% and 21%.

A study with 2×2,400 I.U. anti Xa per day included a comparison with placebo. The frequencies of thrombosis were 12% and 42%. No differences were seen between the heparins in respect of hemorrhagic complications.

Dextran

Several causes are assumed for the thrombosis-inhibiting effect of dextran. Dextran brings about an intravascular volume expansion. A hemodilution appears, the venous return is increased, and the rheological conditions in the vascular periphery are improved. There is a loss of function of Factor VIII antigen and of von Willebrand-ristocetin cofactor, which is necessary for platelet aggregation. The Factor VIII activity is not lowered. The platelet adhesiveness is reduced. Dextran influences the structure of the blood clot; thrombi

are more easily lysed. For the prophylaxis of thrombosis dextran with a mean molecular weight of 60–70,000 or else low molecular weight dextran with a mean molecular weight of 40,000 is administered. The majority of investigations have been carried out with higher molecular weight dextran; there are no known reasons why lower molecular weight dextran should be less active. In rare cases anaphylactic reactions, sometimes with a fatal course, occur during dextran infusion, through the presence in the organism of pre-existing dextran-reactive antibodies. The antibodies can be neutralized by the previous injection of hapten (dextran 1 with mean molecular weight of about 1,000; trade name Promit). 500 ml dextran is given intraoperatively beginning with the anesthetic. A further 500 ml is administered on the same day with a duration of 2–6 h. On the first postoperative day once again 500–1,000 ml dextran is infused and with that, after a total of 1,500–2,000 ml infused dextran solution the thrombosis prophylaxis is ended. Some authors infuse a further 500 ml on the second or third postoperative day. After elective hip operations the thrombosis frequency of 50% could be reduced to about 20%. After fracture of the limbs the thrombosis frequency could also be reduced. In other operative interventions the reduction of postoperative deep vein thrombosis is less convincing. But under dextran prophylaxis a highly significant 5–6-fold reduction of fatal pulmonary embolisms occurs (Table 6). This may be connected with the fact that although thromboses indeed occur, they are nevertheless very light and are rapidly lysed. If dextran

Table 6. Frequency of fatal pulmonary embolism (PE) in thrombosis prophylaxis with dextran 70 or "low-dose" heparin administration (Fischer, 1977)

		Controls		Prophylaxis group		Significance
			Death from PE		Death from PE	
Dextran 70	n	1238	27	1196	5	
8 publications	%		2.2		0.4	$p < 0.001$
Low-dose Heparin	n	1631	18	1610	6	
10 publications	%		1.1		0.4	$p < 0.05$
Kakkar (1975)	n	2075	16	2045	2	
Low-dose heparin	%		0.8		0.1	$p < 0.005$

and "low dose" heparin are simultaneously administered, e.g. in the treatment of patients with stroke attacks, an increased bleeding tendency must be anticipated. Systematic investigations on thrombosis prophylaxis with dextran in internal medicine patients do not exist. Nevertheless, one can deduce that the infusion of about 500 ml dextran in the first 2–3 days, and then every 2–3 days can actively reduce the incidence of thrombosis (Gruber, 1981a, 1981b)

Aggregation Inhibitors

The majority of the investigations have been carried out in surgery and with acetylsalicylic acid, a smaller number with dipyridamole or sulfinpyrazone. The reflection that venous thromboses should also be started by platelet aggregates supports the potential thrombus-inhibiting effect of aggregation inhibitors. By the administration of the above-mentioned aggregation inhibitors alone, no prophylactic effect relative to the occurrence of postoperative venous thromboses could be observed with the help of the radiofibrinogen test (Table 7). No adequate evidence resulted for a reduction of pulmonary embolisms. With the simultaneous administration of acetylsalicylic acid and dipyridamole in general surgical patients a significant reduction of the rate of venous thrombosis compared with the controls was observed. In hip surgery no convincing effect could be demonstrated.
By combination of acetylsalicylic acid with "low dose" heparin, only a small additional reduction of the frequency of thrombosis

Table 7. Occurrence of postoperative deep vein thromboses (DVT) in untreated controls and under acetylsalicylic-lysine in different doses (Schöndorf et al. 1978)

Dose	Controls	Acetylsalicylic-lysine		
		0.9 g/48 h	1.8 g/day	3.6 g/day
No. of patients	15	30	33	30
Patients with DVT	9 (60%)	16 (53%)	19 (58%)	19 (63%)
Bilateral DVT	3 (20%)	5 (17%)	4 (12%)	6 (20%)
DVT popliteal-femoral vein	6 (40%)	8 (27%)	8 (24%)	9 (30%)

could be obtained. However, there was increased postoperative bleeding. Venous thrombosis prophylaxis with aggregation inhibitors can therefore not be recommended, either in surgery or in internal medicine.

Hemorrhage in the child through birth trauma can occur in women who have received acetylsalicylic acid within the last 5 days before parturition, and probably also other antiphlogistics, on account of thrombophlebitis or on other grounds. Increased blood loss during parturition was also observed in the mother during these cases. If the intake of acetylsalicylic acid was discontinued 5–10 days before birth, no increased bleeding tendency was detected in the newborn child. If the drug was taken immediately post-partum, no hemostasis defect could be detected in the child during the nursing period (Schöndorf, 1978, 1980; Stuart et al. 1982)

Coumarins

Coumarins are the drugs of choice in essential long-term anticoagulation. They have their established status in internal medicine in thrombosis prophylaxis. An initially started "low dose" heparin prophylaxis is continued, when long-term anticoagulation is necessary, until the prothrombin time has fallen to the therapeutic range, due to the delayed-action coumarin effect. The indication for long-duration anticoagulation is given with all the risk factors quoted above for the occurrence of thrombosis. In the surgical specialities, perioperatively introduced thrombosis prophylaxis with coumarin alone has been abandoned in favor of "low dose" heparin prophylaxis, on account of the poor controllability and the bleeding tendency. With an only moderate decrease of the Quick value by coumarin there is no thrombosis protection. With adequate preoperatively started anticoagulation, the prophylactic action is comparable with "low dose" heparin administration. After hip-surgical interventions the thrombosis frequency sank from 56% in the control group to 33% in the prophylaxis group. In earlier investigations the postoperative mortality due to lung embolism could be decreased from 0.51% to 0.06%. The postoperatively started anticoagulation does not offer sufficient protection. Complications due to bleeding occur in 7% of cases when coumarin prophylaxis is initiated preoperatively and in 4.5% of cases when

begun postoperatively (Dick et al. 1959, 1961; Schöndorf 1981; Sevitt and Gallagher 1959).

Treatment of Venous Thrombosis

Methods of treatment include thrombectomy, fibrinolysis and anticoagulation therapy with heparin and coumarin derivates.

Thrombectomy

Surgery is considered only in the event of thrombosis of the pelvic and proximal crural veins. The results of surgery are adequate only in the first 5–8 days at maximum, when the thrombus is still recent and before it becomes attached to the vessel walls and organization processes begin to take effect. Ideally, it is possible to achieve complete reestablishment of circulation. In 60%–80% of patients who undergo thrombectomy according to strict indications, it should be possible to avoid postthrombotic syndrome. With phlegmasia coerulea dolens, surgery can represent a means of preserving the limb. Surgical indications are based on the nature of the primary illness, contraindications for alternative modes of treatment such as fibrinolysis or anticoagulation therapy, the patient's age and the degree of postthrombotic syndrome anticipated (Brücke 1981b).

Fibrinolysis

The goal of fibrinolysis is to reestablish venous circulation and to preserve the valves as much as possible in order to prevent postthrombotic syndrome, which develops over a period of months or even years.
The indications for fibrinolysis therapy are dependent amongst others on the age of the patient with the chance of a postthrombotic syndrome, and with it the consequence of falling ill. 250,000 I.U. streptokinase are sufficient as initial dose in about 85% of patients. The therapy is continued with 100,000 I.U. or two thirds to a half of the initial dose per hour; after 36–48 h through consumption of plasmino-

gen a reduction of the lysis effect detectable by coagulation analysis can be observed, with decrease of fibrin-fibrinogen split products in the plasma and shortening of the thrombin, reptilase and activated partial thromboplastin times. An additional heparin treatment with 10,000–20,000 I.U. per day is necessary for the inhibition of re-thrombosis. The thrombin time should be prolonged to 2–4 times normal. The duration of lysis is prolonged one day beyond the clinical result. Streptokinase therapy cannot be carried out beyond 5–7 days, because it is ineffective due to the increasing antistreptokinase titer in the blood. The treatment can be continued with urokinase. The initial dose for the neutralization of the kinase inhibitors is 200,000–600,000 I.U. with urokinase, higher than with streptokinase. There are various ideas at the present time on the hourly dose of urokinase to be given subsequently. This amounts to 40,000–100,000 I.U., but also up to 200,000 I.U. per hour is recommended. With lower doses clearly worse results are obtained. On account of the absence of antigenicity, urokinase treatment can clearly be carried on indefinitely. Because at least in lower doses only a small fibrinolytic effect is demonstrable systemically, as a rule an accompanying heparin administration of 10,000 to 20,000 I.U./day is necessary.

It is generally true that proximally occurring thromboses are more easily accessible to fibrinolysis than peripheral thrombose. Lower-leg venous thromboses have up to 7 days after their formation a real chance to become lysed. Thrombolysis should only be carried out when several vessels are closed. Thromboses of the popliteal, femoral and iliac veins are still accessible to successful lysis after 6–14 days. However, the re-opening rate clearly decreases 6–9 days after the formation of a thrombus. Moreover, it must be taken into account that a thrombosis is first diagnosed clinically 2–4 days after its occurrence. The lysis begins after about 2–4 days. Also thromboses with an age of several weeks up to 3 and even 6 months may in individual cases be successfully lysed. A complete and a partial reopening occurs with fresh thrombi within the first 3 days after their occurrence in about 90%, and within the first 7 to 9 days in 71–82%. In thromboses with an age of 4 to 8 weeks it is possible as a rule only to obtain partial opening in 55–80%.

In so-called late lysis with a venous occlusion duration of between 14 days and 6 months a phlebographically demonstrable result was recorded in 16% and a partial result in 5%. Through prolongation of

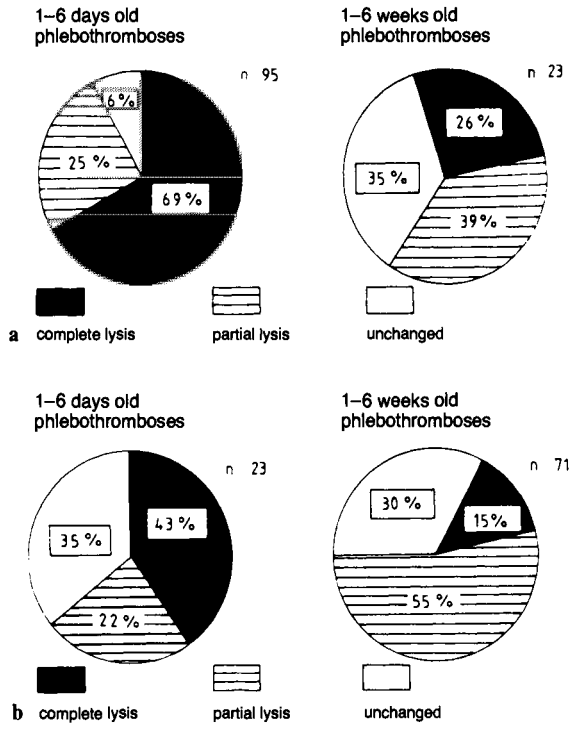

Fig. 2a, b. a) Results of streptokinase therapy in acute and older deep vein thromboses; **b)** Results of urokinase therapy in acute and older deep vein thromboses (Trübestein 1982)

the duration of lysis with urokinase up to 21 days a small increase of the reopening rate of an additional 4 or 2% was observed. The success rates of different authors are presented in Fig. 2 and Table 8. Depending on the form of the operative intervention, a postoperative thrombolysis should not take place before the 7–14th day after the operation, due to the increased bleeding risk. An apoplectic insult or an operative intervention on the central nervous must be longer than 6 weeks ago. Under heparin therapy after 8 days only in about 10% of patients is a partial spontaneous lysis demonstrable phlebographically.

Table 8a, b. a) Results of urokinase therapy in acute leg-vein thromboses
b) Results of urokinase therapy in older deep vein thromboses (Zimmermann et al., 1983)

a) Authors	n	Age of thrombosis (Days)	Urokinase IU/24 h	Treatment duration (Days)	Recanalization		
					Complete	Partial	None
Juhan 1979	29	?	ca. 3.5 million	2	–	26%	74%
Trübestein 1981	19	1–6	ca. 1.5 million	10	37%	21%	42%
Zimmermann 1982	31	1–10	1.5–2 million	10	31%	30%	39%
			2,000 I. U./kg/hr. (initial)	10	43%	33%	24%

b) Authors	n	Age of thrombosis (Days)	Urokinase IU/24 h	Treatment duration (Days)	Recanalization		
					Complete	Partial	None
Tilsner 1980*	187	14–180	1–1.5 million	– 21	37%	12%	51%
Trübestein 1981	52	7– 42	ca. 1.5 million	– 20	17%	52%	31%
Zimmermann 1982	58	11– 42	ca. 2 million	– 14	13%	21%	66%

* In part a pretreatment with streptokinase occurred

The indications for fibrinolysis treatment in pregnancy must conform to particularly strict criteria. It can be justified in an pocclusive iliofemoral thrombosis in which the incidence of a consecutive pulmonary embolism amounts to 13%, and also in pulmonary embolism. In the last case the fibrinolysis treatment is all the more to be justified, because the maternal indication outweighs that of the child. Streptokinase does not seem to be transferred into the fetal circulation, so that a hemostasis defect is not induced in the child. Whether urokinase or the maternal fibrin/fibrinogen cleavage products pass the placental barrier and induce a hemostasis disorder in the child, is not known. A fibrinolysis treatment must not be carried out before the 9th week of pregnancy because up to this point of time still no complete stabilization of the placenta has occurred, as far as the fibrin is concerned. After the 14th week of pregnancy there is no longer any danger of this. The therapy can be carried out up to the 40th week of pregnancy, during which however the danger of the occurrence of a retroplacental hematoma exists. If a thrombosis occurs in the puerperium, in uncomplicated birth fibrinolysis treatment can be begun immediately post partum. In vaginal or abdominal hysterectomy a latency period of 10–14 days is to be adhered to, which under some circumstances must be bridged over with heparin.

A complication of thrombosis treatment of deep pelvic-leg vein is pulmonary embolism. It is thought to occur in 4–8% of cases and in 1–2% progresses fatally. A significant difference does not occur with heparin treatment. Under some circumstances one should, with free-floating thrombi with long thrombus heads in the pelvis region, despite good lysability, avoid thrombolysis on account of the danger of pulmonary embolism. Under streptokinase therapy – but for chronic arterial stenoses and occlusions, and not for venous thromboses – hemorrhages were recorded in 29.5% of cases. In 7.5% of cases it necessitated the breaking off of therapy. Hemorrhages after streptokinase occurred with increased frequency after 3–6 days. Hemorrhages under urokinase are less common. Fibrinolysis treatment has to be discontinued in about 14% of cases in total (due to hemorrhage, fever, high antistreptokinase titer) (Schmutzler, R., 1981b; Tilsner, 1975)

If a venous thrombosis occurs, anticoagulation with subcutaneous "low dose" heparin is no longer sufficient to stop the growth of the thrombus and to inhibit a pulmonary embolism. If fibrinolysis therapy is not indicated intravenous heparin therapy must now be carried out. Initially a bolus of 5,000 I. U. to 10,000 I. U. heparin or 75 I. U. to 150 I. U./kg body weight is given and then an intravenous infusion is given by a perfusor, in a dose of 20–40,000 I. U./day, corresponding to about 300–500 I. U./kg body weight. The amount of heparin to be infused is adjusted by the thrombin time or the activated partial thromboplastin time prolongation, which must amount to at least 2–4 times the normal value. Immediately after operations, after extensive and multiple injuries with strongly increased risk of hemorrhage as well as severe bleeding sites which can be overlooked, the initial dose of 2,500–5,000 I. U. is to be halved or omitted, and a subsequent reduced daily dosage of 7,500–10,000 I. U. heparin, corresponding to 100 I. U. to 150 I. U./kg body weight and 24 h is advisable.

With extensive thromboses in the postoperative phase, and in long-duration high-dose heparin therapy a decrease of antithrombin III -level with increasing reduction of the anticoagulatory action of heparin can occur. This expresses itself in coagulation analysis as an increased shortening of the thrombin time or activated thromboplastin time. If the thrombin time sinks below about 30 s, the substitution of antithrombin III concentrate in a daily dosage of about 2,000 U is necessary. The intravenous intermittent heparin administration in 4 to 6 hourly intervals in a dose of in total 20,000–40,000 I. U./day corresponding to 300–500 I. U. heparin/kg body weight and day is a possible alternative. On account of the strongly varying plasma heparin level and consecutive varying antithrombotic action as well as the increased bleeding risk continuous administration is to be preferred.

Heparin action can be immediately blocked by protamine chloride or protamine sulfate. 1–1.5 mg protamine neutralizes 100 I. U. heparin. After 2–6 h a repeated protamine administration in half or one-third the initial dose becomes necessary.

Low molecular weight heparin (LMW-heparin) is given once daily subcutaneously in a dose of between 5,000 and 10,000 I. U. anti Xa (maximal 20000 I. U. anti Xa) for the treatment of manifest thrombosis. The plasma level of anti Xa rises to 1.0 I. U. per ml, the aPTT is

prolonged by about 30% of the baseline values. Alternatively 2,400 I. U. anti Xa per kg bodyweight and day are infused. The anti Xa level in the plasma similarly lies at 1.0 I. U. Doubling the daily dose leads to an unacceptable frequency of bleeding.

After 8–12 days, when a fixation of the thrombus to the vessel wall can be assumed, transference of heparin therapy to therapy with anticoagulants of coumarin type should take place. On account of the delayed occurrence of anticoagulatory action of coumarin derivatives, overlapping change must take place until the prothrombin time is in the therapeutic range. On the first day 4–6 tablets of phenprocoumon (Marcumar) corresponding to 12–18 mg, are given, and on the second day, 2–3 tablets, corresponding to 6–9 mg. In the ensuing days, the dosing is controlled by individual need. The therapeutic action is attained after 2–3 days. After withdrawal the prothrombin time is no longer in the therapeutic range after 2–5 days. Anticoagulatory protection then no longer exists. According to the drug used, 8–14 days is required before the prothrombin time has again normalized itself (Table 1/XIV). In rare cases a coumarin resistance occurs. Attention is to be paid to interactions with other drugs which either strengthen or weaken the action of the anticoagulant. In uncomplicated thrombosis the duration of treatment amounts to 3–6 months. In about 24% there is with heparin and Marcumar therapy a complete (but mainly however only incomplete) recanalization. After pulmonary embolism, thrombectomy and thrombolysis the anticoagulation must be extended to 1 year. In protein C, antithrombin III deficiency, recurrent venous thromboses and/or pulmonary embolism, heart insufficiency and other conditions with elevated risk the anticoagulation under certain circumstances must continue for life.

As antidotes prothrombin complex preparations and vitamin K_1 (Konakion) are available. In the immediate post-partum use of coumarin derivatives it must be realised that these can be transferred into the maternal milk and produce a hemostatic defect in the newborn child. The danger of an anticoagulation of the child seems rather small however. It must be remembered that in the child immediately after birth the synthesis of prothrombin complexes and of fibrinogen is quantitatively and qualitatively still limited and in the first days there is a physiologically increased bleeding tendency. If in patients under oral anticoagulation an operative intervention is necessary or if trauma occurs, the following procedure recommends itself. (see Chapter VII).

If sufficient time is available one allows the Quick value in major operations to increase to over 50% of normal. The operation takes place under the protection of subcutaneous "low dose" heparin prophylaxis. After 5–10 mg Konakion per os or intravenously a clear shortening of the prothrombin time is to be expected after 6–10 hours. For immediate normalization of hemostasis initially 1,000–3,000 U of a prothrombin complex preparation is to be administered. Corresponding to the half-life of the coagulation factors, renewed substituton therapy must be carried out at 6–8 h intervals, until the patients own prothrombin complex synthesis suffices for hemostasis. The thrombogenicity of numerous prothrombin complex preparations presents a risk. After bleeding under anticoagulants, factor substitution by means of fresh blood, fresh plasma, and fresh frozen plasma is available.

Phlegmasia Coerulea Dolens, Phlegmasia Alba Dolens

In phlegmasia coerulea dolens a complete or an almost complete occlusion of the venous vascular cross-section of the affected extremity, usually one leg, occurs. Besides the thrombotic occlusion of the deep pelvic and leg veins there is also a thrombosis of the venules. The clinical symptomatology is caused by high-grade venous flow disorders. It imposes a blue-staining of the entire extremity and an increasing edema. The full picture of the phlegmasia occurs relatively acutely. Frequently in the previous days and weeks inflammatory processes in the veins and thromboses with partial flow path obstruction have occurred. Not uncommonly the phlegmasia is a paraneoplastic syndrome of tumors which lie in the pelvic region. A secondary compression of the arterial vascular system as a consequence of increasing edema is frequent. Phlegmasia alba dolens is an expression of a predominantly arterial flow-path obstruction, and a high-grade flow delay as a consequence of edema of the extremity. In the affected extremity several liters of fluid can accumulate, so that hypovolemic shock can occur. For the prevention of the latter and the threatened gangrene rapid intervention is necessary. The method of choice in diseases of the lower extremity is surgical intervention with thrombectomy of the femoral vein in a proximal and distal direction up to the popliteal vein.

In spite of further existing occlusion of the further peripherally situated veins a sufficient perfusion of the extremity is thus attained.
If there are contraindications to operative intervention or less acute symptomatology fibrinolytic treatment can be carried out with initially 250,000 I. U. streptokinase in 20 min., and a maintenance dose of 100,000 I. U. to 150,000 I. U./hour. For the elimination of peripherally situated thrombi, especially in the lower limb, a combined procedure of operation and regional fibrinolysis of the affected extremity after cannulation of the arteria and vena femoralis, with the setting up of an extracorporeal circulation and exclusion of the extremity from the systemic circulation has been proposed. The perfusion runs over 60–90 min. with a perfusion flow rate of 300–600 ml/min. To the perfusing blood 25,000 I. U.–30,000 I. U. of Streptase is added. With each of these therapeutic measures a heparin treatment is carried out over a period of 8–10 days, which is then transferred to anticoagulation with coumarin derivatives.

Thromboembolic Occlusion of the Retinal Vessels

The causes of an occlusion of the retinal vessels are various. With a central vein thrombosis frequently pathological-anatomical causes can be found. Heart failure and polycythemia are predisposing factors; central venous thromboses occur occasionally with accompanying changes in the central artery. In a central arterial thrombosis cardiac failure, polycythemias as well as hypertension and arteriosclerotic changes of the vessels come into consideration as promoting factors. Emboli in the retinal artery take their origin from arteriosclerotic plaques of the extra- and intracranial carotid bloodstream. Fibrinolytic treatment in the usual dosage should if possible be started within the first hours after the beginning of clinical symptomatology with loss of vision and haziness before the eyes. Irreversibility of the damage and risk of hemorrhages are to be expected within a few hours. Treatment has been successfully carried out up to 7 days after the occurrence of thrombosis in the retinal vessels. Contraindications such as progressive arteriosclerosis and hypertension are strictly to be observed in the patients, who are mainly elderly. A fibrinolysis is carried out for 1–2 days. Following this the patients are anticoagulated with heparin and then with coumarin derivatives for at least a half-

year. The success rate of the fibrinolysis treatment should be about 30%. If contraindications exist for fibrinolysis treatment, anticoagulation with intravenous heparin is carried out over several days, and then the patient is transferred to oral anticoagulation. A clinical improvement occurs in about the same frequency as with fibrinolysis treatment, so that the latter should be reserved for special cases.

Pulmonary Embolism

Pathogenesis and Clinical Features

Several grades of severity of pulmonary embolism are distinguished. According to clinical, hemodynamic, and blood-gas measurement criteria mild (Stage I), submassive (Stage II), massive (Stage III), and fulminant (Stage IV) embolisms are distinguished (Table 9).
The fulminant lung embolism ends fatally in each case within a few minutes to ½ an hour (Fig. 3). There is a complete blocking of the pulmonary trunk and/or both main branches of the pulmonary artery, a blocking of a main trunk and large branch on the opposite side, or on the other hand the blocking of several large branches in both lungs.

Table 9. Grades of severity of lung embolization with corresponding therapy (Lasch, Oehler 1982)

	Small embolism	Submassive embolism	Massive embolism	Fulminant embolism
Obturation of lung vascular cross-section	< 50%	< 50%	> 50%	> 70%
Circulation	No essential findings	Tachycardia RR lowering	Early to fully developed shock	
P_{O_2} (mm Hg)	Normal	< 80	< 60	< 50
P_{CO_2} (mm Hg)	Normal	< 35	< 30	< 30
Therapy	Heparin	Heparin → Fibrinolysis		Embolectomy

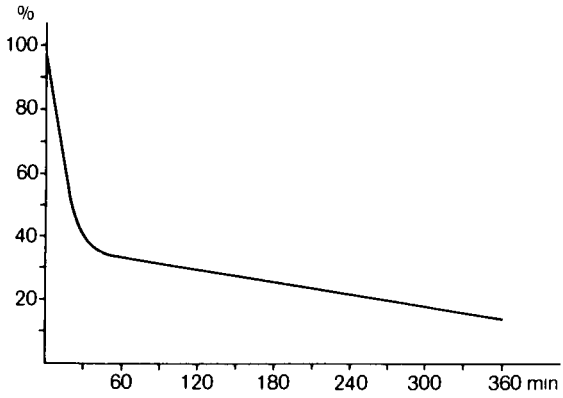

Fig. 3. Dependency of lethality in massive and fulminant pulmonary embolization (Stages III and VI) on the time of occurrence of clinical symptomatology (Heinrich, Klink 1981)

More than 65–70% of the vascular cross-section is blocked. With the massive embolism, in which there is a lethality of 65% within the first 30 minutes, 50% and more of the blood flow path is blocked. With submassive lung embolisms the cross-sectional blocking is under 50%. In about one third of the cases small lung embolisms precede the large lung embolism. In about 70% of the patients clinical evidence for the occurrence of deep venous thrombosis is missed. Small recurrent emboli can occur over weeks and months and lead to chronic cor pulmonale. In about 50% of the cases there is a hemorrhagic lung infarct. Clinically small emboli are mainly inconspicuous. Submassive emboli are accompanied by tachycardia and hyperventilation, massive emboli with dyspnoea, with and without shock symptomatology, fulminant emboli with dyspnoea, shock and cardiac arrest. In the last case the time until death occurs is frequently so short that shock symptomatology cannot develop. The arterial blood pressure is facultatively lowered in submassive embolism, with massive and fulminant embolism lowered in every case.

In massive and fulminant embolization the pulmonary artery mean pressure lies above 30 mm Hg. The arterial oxygen tension decreases with increasing grades of severity to from under 80 to under 50 mm Hg. Similarly the arterial carbon dioxide tension sinks to 30 mm Hg and below. If sufficient time is available, pulmonary angiography gives the

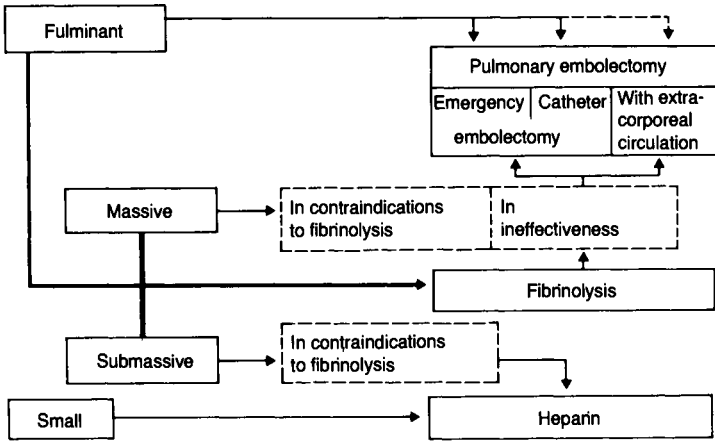

Fig. 4. Possibilities of therapy in pulmonary embolism (Heinrich, Klink 1981)

most exact information on the extent of the embolization. Perfusion and inhalation scintigrams are further informative parameters. The conventional X-ray gives the most uncertain information. The therapeutic procedure depends on the clinical picture, the course and the extent of the pulmonary blood flow obstruction (Fig. 4) (Heinrich, Klink, 1981).

Therapy

Pulmonary Embolectomy

Pulmonary embolectomy without extracorporeal circulation should only be carried out in extreme cases. Only centrally situated emboli are accessible. By the setting up of extracorporeal circulation worthwhile time can be gained. The indications for embolectomy consist of cardiac arrest refractory to reanimation and refractory shock under fibrinolysis therapy. A current or immediately preceding fibrinolysis is no contraindication for an operation.

The mortality with setting up of an extracorporeal circulation amounts to 29–57%, without bypass to 90%. In a comparison of different forms

of therapy of massive embolization with shock symptomatology the results after embolectomy and streptokinase therapy are about the same. Heparin therapy cuts out the worst. According to other classifications with comparable severity grades of pulmonary embolism, the lethality of the thrombolysis group with 18% is clearly lower in comparison to the embolectomy group with 32–63%. Only a few result reports are available on the success rate of the so-called catheter embolectomy. By means of a catheter lying in the pulmonary artery a local fibrinolysis can be inserted before or after the embolectomy (Heinrich, Klink, 1981).

Fibrinolysis and Anticoagulants

In the pulmonary flow path there exists a high tendency to spontaneous lysis, the rate of which is not sufficient however to positively influence the acute disease picture. The purpose of thrombolysis treatment is the dissolution or diminution in size of the pulmonary embolus with simultaneous fibrinolysis of the residual thrombus at the original site of the embolization. An essential additional therapeutic aspect is the positive influence on a simultaneously occurring shock condition by fibrinogenolysis with consecutive improvement of the shock-conditioned microcirculatory disorder. Fibrinogenolysis is indicated in fulminant lung embolism without the possibility of an embolectomy. In massive lung embolism with accompanying shock symptomatology fibrinolysis treatment is immediately to be instituted and the preparations for an immediate operation are to be made. The course under fibrinolysis in the first hour decides whether an embolectomy is necessary. This is indicated as mentioned by sudden cardiac arrest and continuing shock symptomatology. The same procedure applies to submassive pulmonary embolism with shock symptomatology. In a submassive embolic process without shock symptomatology fibrinolysis treatment with due regard to the contraindications is the method of choice. Small pulmonary emboli are treated with the intravenous administration of heparin. Fibrinolysis treatment comes into consideration in recurrent embolization under heparin.

A comparison of fibrinolysis with heparin therapy over a period between 12 and 24 h as well as an investigation series over 72 h shows a rapid improvement of the hemodynamics under fibrinolysis. The dis-

solution of the thrombus progressed further after 24 h under fibrinolysis than under heprain. There was no difference between 12 h and 24 h fibrinolysis and between urokinase and streptokinase. After 2 weeks the lung scintigrams of the fibrinolysis group and the heparin group were similar, which testifies to the high spontaneous lysis capability of the pulmonary vascular system. The mortality in the heparin and fibrinolysis groups at 9 or 7% were not different. From this it appears that if relatively mild or moderately severe embolizations are treated, their chance of survival per se is already relatively good (Sasahara et al., 1973, 1975a, 1975b). Streptokinase and urokinase treatment are commenced with 250,000 U within 10–20 minutes. Higher initial doses of streptokinase and urokinase of 600,000 I. U. or with urokinase of 1,000,000 I. U. have been recommended. The continuation dose for both fibrinolytics amounts to 100,000 I. U.–200,000 I. U., with urokinase up to 300,000 I. U., per hour. The duration of fibrinolysis depends on the clinical picture and amounts to between 1 and 3 days. Fibrinolysis therapy can be combined with 10,000–20,000 I. U. heparin. Pulmonary emboli of varying degrees of severity were successfully treated according to clinical and angiographic criteria with both 15,000 I. U. urokinase per kg bodyweight given as a bolus injection over 10 minutes into the right atrium, and also with tissue plasminogen activator in a dose of 50 mg given intravenously for 2 hours, and if necessary with 40 mg for another 4 hours. After the ending of fibrinolysis, therapy is continued with 20–40,000 I. U. heparin/day as an infusion for 6–14 days, and then transferred to coumarin derivatives. With heparin therapy alone, after an initial bolus of 10–20,000 I. U., therapy is continued with 20–60,000 I. U. day. The heparin therapy inhibits the appositional growth of the thrombi in the initial region and in the pulmonary circulation: it therby gains time for the physiological fibrinolytic process. The anticoagulation with heparin is also carried out in this case over 6–14 days. There after follows the transition to oral anticoagulation for a mean of 12 months. The implantation of a cava clip or a umbrella filter to prevent recurrent thromboembolism does not make anticoagulation superfluous.

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IX. Coronary Thrombosis and Myocardial Infarction

Definition, Etiology, Pathogenesis

If the oxygen supply falls below the current myocardial oxygen requirements for any length of time, this results in a general impairment of function with or without a disseminated destruction of the cardiac musculature or a myocardial infarction with a localized loss of myocardial function. One of the most important preconditions for the occurrence of an acute cardiac infarction is a stenosis of a coronary artery of 75% or more of its cross-sectional area. The acute event in the myocardium can be induced by a great number of extracardiac and cardiac pathological mechanisms: anemia, hypotension, shock, altered rheological properties of the blood such as paraproteinemias and polycythemia, cardiac arrhythmias etc. Transient spasms of the coronary arteries similarly lead to myocardial ischemia (Prinzmetal-angina). Even in the absence of angiographically demonstrable stenoses or occlusions of the coronary arteries disorders in the microcirculation can be the cause of ischemic events in the myocardium. This can occur through pathological changes of the terminal circulation in hypertension, autoaggressive diseases and endotoxinemia, as also through rheological changes in the course of autoaggressive diseases, paraproteinemias, polycythemia etc. Arrhythmias and acute ischemia syndromes can be induced through thrombocyte aggregates which become detached from arteriosclerotic plaques of the coronary arteries and are carried into the peripheral vascular region, but also through platelet aggregates which have developed in the systemic vascular system and have been transported into the coronary vessel system in general hypercoagulability, diabetes and hyperlipidemias. Emboli from thrombocyte aggregates in the coronary peripheral vas-

cular region are often said to be the cause of cases of sudden heart death.

Opinions vary as to the pathogenetic significance of an acute subtotal or total occlusive coronary thrombosis located in an arteriosclerotically altered coronary vessel for the development of a myocardial infarction. The question is whether the occlusive coronary thrombi demonstrable at autopsy developed before the infarction as its cause, or only after the infarction event in the context of the general hypercoagulability of the blood. Morphologically the thromboses largely appear as red, fibrin-rich coagulation thrombi. The data given for the frequency of occlusive coronary thromboses in autopsy material fluctuate between 15 and 95%. There is a relationship between the size of the infarcted area and the presence of a thrombosis. The following reasons have been adduced, inter alia, in favour of the view that the coronary thrombosis first occurs after the infarction event. As the survival time of the patient increases after an infarction, there is an increase in the number of demonstrable thrombi. In patients who die relatively shortly after an ischemia of the myocardium, an occlusive thrombus could relatively rarely be demonstrated. In patients with cardiogenic shock, thrombi were found more often at autopsy in those who died from this than in patients who died without shock. This was interpreted along the lines that the deposition of fibrin in the arteriosclerotically altered coronary vessel first occurred in the context of the shock-induced activation of coagulation. It could also be demonstrated at autopsy that radioactive fibrinogen, which was administered to the patients post infarction, was taken up into the coronary thrombus. This was also interpreted as showing a post infarction genesis of the coronary thrombus.

Although it seems entirely plausible that coronary thrombi might have developed or become larger after the infarction, the interpretations of the findings described do not stand up to criticism in all points. The fact that patients who died relatively early after the onset of an infarction often did not have any thrombi might be due to the circumstance that the infarction had occurred through arrhythmias with a fall in the cardiac output to below the critical limit, through an acute fall in the blood pressure etc., and thus in a fundamentally different way. Radioactively labelled fibrin and fibrin split products are able to penetrate into a preformed thrombus and to accumulate in it. The demonstration of radioactivity in the thrombus thus does not necessar-

ily mean that it developed after infarction. Moreover it has been shown that radioactively labelled fibrinogen which was administered intravenously after infarction could not be demonstrated in the central sections of the occlusive coronary artery thrombus. This suggests the pre-existence of the thrombotic occlusion and merely permits of the possibility of a post infarction apposition.

In patients who have examined angiographically within the first 4 h after the onset of symptoms, a complete occlusion of the coronary artery can be demonstrated in 87%. In patients who have an angiogram taken within 12–24 h after the onset of infarction, a complete occlusion can be demonstrated in only 65% still (De Wood et al., 1980). In 15–25% of patients the first angiography after an acute myocardial infarction showed only subtotal occlusion of the coronary artery in question. The percentage of incompletely occluded vessels increases with the interval of time between the angiography and the infarction event from less than 15% within the first 6 h to about 35% after 12–24 h. This can be interpreted as the spontaneous fibrinolysis of an initially completely occlusive thrombus.

To sum up it can be said that in 80–90% of cases a coronary thrombosis shows a direct chronological relationship with the infarction event and that spontaneous recanalization can be expected in a certain percentage of cases. The development of thromboses is not confined to the coronary vessel system however. The systemic hypercoagulability after an infarction promotes the occurrence of thromboses in the veins of the pelvis/leg region, of mural thromboses over the infarction area, of thromboses in the arterial vessel system and promotes the development of a disseminated intravascular coagulation in cardiogenic shock. The fibrinolysis treatment and anticoagulation with heparin and coumarin derivatives are aimed at the elimination or prevention of the thrombotic events described with the object of limiting the size of the infarction, of improving the hemodynamics and of preventing secondary thromboembolic complications.

Treatment

Fibrinolytic and Thrombolytic Therapy of Acute Myocardial Infarction

The fibrinolytic treatment of acute myocardial infarction is aimed at preventing the development of a reversible into an irreversible

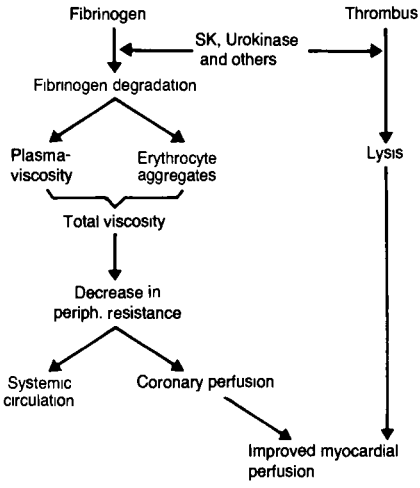

Fig. 1. Possible mechanisms of action of fibrinolytic therapy for acute myocardial infarction (Kirchoff, van de Loo, 1981)

ischemia, through early reperfusion of the affected muscle area, at reducing the size of the infarction and at maintaining the pump function of the heart as far as possible. There are many ideas about how this objective can be achieved through fibrinolysis, and these have been variously assessed in the course of the years (Fig. 1).

The recanalization of the thrombotically occluded coronary vessel is said to prevent the infarction or at least limit the size of the infarction with maximal preservation of contractile substance. The elimination of possible microthrombi in the marginal areas of the infarction with a consecutive improvement in myocardial perfusion pursues the same objective. The degradation of circulating fibrinogen/fibrin monomer complexes, which can be demonstrated in the context of the systemic hypercoagulability after infarction, can prevent the apposition and new occurrence of thrombi in the vessel system of the heart. A prerequisite in every case is that the fibrinolysis should commence at the earliest possible time. An improvement in the rheological properties of the blood induced through the fibrinolysis can improve both the myocardial perfusion and also the peripheral microcirculation and thus create more favorable conditions for the hemodynamics after

infarction. The increased viscosity of the blood following infarction is partly due to the circulating fibrinogen/fibrin monomer complexes. The degradation of fibrinogen and the fibrin polymers to split products inhibits the fibrin polymerization and reduces the aggregation of thrombocytes and erythrocytes. As a result of this the nutritive supply to the peripheral vascular region is increased. This is of particular importance in circulatory centralization and cardiogenic shock. Another positive effect is the clearance of microthrombi in the peripheral vascular region, which develop in the context of the shock-induced diffuse intravascular coagulation processes.

Systemic Fibrinolysis

The beneficial action of fibrinolysis on the hemodynamic parameters by comparison with heparin therapy has been documented in patients with myocardial infarction (Neuhof et al., 1975) (Fig. 2, Fig. 3). The study comprised patients whose infarction had commenced not longer than 12 h previously.

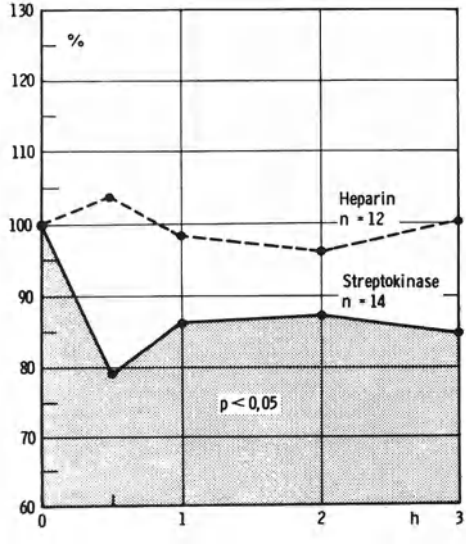

Fig. 2. Change in the total peripheral resistance of patients with acute myocardial infarction and treatment with streptokinase or heparin (Neuhof et al., 1975).

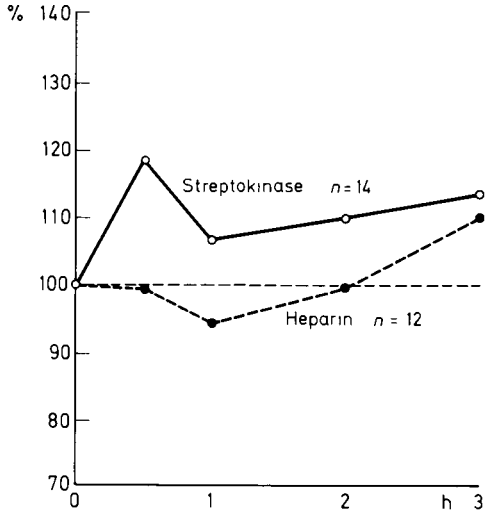

Fig. 3. Change in the oxygen uptake of patients with acute myocardial infarction and treatment with streptokinase or heparin (patients not in shock; difference not significant) (Neuhof et al., 1975)

One group of 14 patients received 250,000 I.U. of streptokinase within 20 min and following this 100,000 I.U. per hour for another 24 h. The other 12 patients received heparin in a dose of 20,000–30,000 I.U./24 h. The hemodynamic parameters were measured for 48 h. Significant differences between the two groups were only obtained within the first 3 h. The peripheral resistance fell significantly in the streptokinase group, the mean arterial pressure decreased and the cardiac output increased. The heparin group did not show any changes by comparison with the baseline value. The oxygen uptake showed no differences in the groups of patients. A state of shock was not present. In individual observations of patients with cardiogenic shock an improvement was seen in the oxygen uptake under streptokinase as a sign of a restored microcirculation (Fig. 4).

These investigations prove a therapeutic principle. Findings have not been obtained on a fairly large group of patients so that no conclusions can be drawn about whether the changes measured in the hemodynamics under streptokinase would have an influence on reducing the lethality after myocardial infarction.

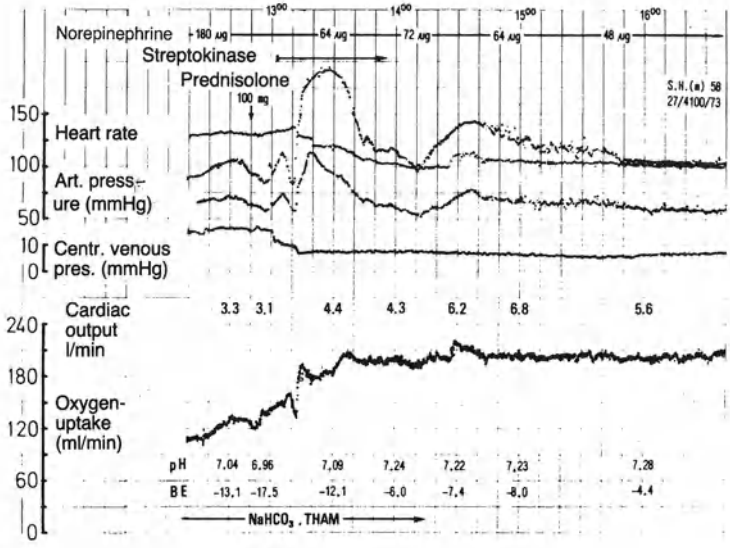

Fig. 4. Serial charts of a 58 year old female patient after myocardial infarction with cardiogenic shock. Action of fibrinolysis therapy on circulatory parameters, oxygen uptake and metabolism (charts made available by Prof. Neuhof)

The therapeutic concept of fibrinolytic treatment with streptokinase in myocardial infarction was introduced into clinical medicine by Fletcher et al. (1958, 1959). Over the past 20 years 20 clinical studies have been published on fibrinolytic therapy in acute myocardial infarction, in which streptokinase was used almost exclusively and urokinase in only a few individual studies. Table 1 gives a synopsis of 12 randomized, prospective streptokinase studies.

The patients were admitted to the study series up to 12 h and up to 24 h after the onset of the infarction. The treatment commenced with an initial dose of 200,000 I.U. to 250,000 I.U. of streptokinase within 20 to 30 minutes and was continued with 100,000 I.U.–150,000 I.U. (200,000 I.U.) per hour over 12–24 h, over 3 h and 72 h in one study each. The period of observation amounted to 40 days, or to 3 months in one case (Australian study) and to 6 months (European study) in

Table 1. Controlled studies on the action of streptokinase therapy in acute myocardial infarction (Genth, 1982)

Clinical studies	No. of patients		Age of infarction	Duration of therapy	Treatment controls	% Lethality		Significance $P < 0.05$
	SK	Controls				SK	Controls	
German/Swiss study I (1966)	297	261	12 h	18 h	Heparin	14.1	21.7	+
European Working Party I (1969)	83	84	72 h	72 h	Heparin	24.1	17.9	−
European Working Party II (1971)	357	339	24 h	24 h	Heparin	19.0	27.4	+
Finnish study (1971)	219	207	72 h	1–48 h	Phenindione	9.0	9.2	−
Italian study (1971)	164	157	12 h	12 h	Heparin	11.6	11.5	−
Danish study (1972)	67	68	24 h	20 h	Phenindione	23.8	29.4	−
Australian study (1973)	230	227	24 h	18 h	Heparin	9.8	12.6	−
German/Swiss study II (1971)	138	131	12 h	18 h	Levulose	14.5	26.0	+
Frankfurt study (1973)	102	104	12 h	3 h	Placebo	12.8	27.6	+
British study (1976)	302	293	24 h	24 h	Placebo	12.6	13.7	−
Austrian study (1977)	352	376	12 h	16 h	–	10.5	15.6	+
European study (1979)	156	159	12 h	24 h	Glucose	15.6	30.8	+

another. In all of the studies in which the infarction was up to 12 h old at the start of the streptokinase therapy, a significant reduction in the lethality was seen; this also applied to the short-term lysis of 3 h (Frankfurt study). When the infarction was aged up to 24 h a positive trend could be demonstrated; a negative result was obtained in one study. A unanimous finding was an earlier regression of the ECG changes by comparison with the control group and also a more premature rise and fall in the CPK. On the whole the studies are not readily comparable since the patients differed in respect of the degree of severity and complications of the infarction.

Special mention needs to be made of the European multi center study published in 1979. Through this the question of the positive effect of fibrinolytic treatment was taken up again. An attempt was made to work out criteria by means of which patients who would particularly benefit from fibrinolysis therapy could be identified. Patients were admitted to the study whose infarction had occurred not more than 24 h previously. Following an initial dose of 250,000 I.U. streptokinase within 20 min, 100,000 I.U. of streptokinase/hour were infused over 24 h. 512 out of 2338 patients were admitted to the study and subdivided into three risk groups. Since the group with the highest risk comprised only 1.6% of the patients admitted to the study, this was combined with the medium risk group to form a total of 315 patients. The group consisted of men and women aged between 50 and 75 years without any contraindications for fibrinolytic therapy. The following were seen as increased risk factors: systolic blood pressure below 90 mm Hg, heart rate below 60 or over 100 beats/min, more than 5 supraventricular or ventricular extrasystoles/minute, QRS complex of 0.12 s or longer, 2nd or 3rd degree AV block, atrial flutter or atrial fibrillation. 156 patients of this group were treated with streptokinase, 159 patients acted as controls. Treatment with coumarin derivatives was commenced on day 1 and carried out for at least 3 weeks. The patients of risk group 1 (least risk) were not treated with streptokinase. The total observation period amounted to 6 months. In the streptokinase group 25 patients (16%) died, whilst in the control group the figure was 50 patients (31%). Thus a 50% decrease in lethality was achieved. A striking finding was that no significant difference was seen in the mortality of the two groups in the first few days after the infarction. Significance ($P < 0.01$) was reached only from the 4th week. A total of 6.1% (total number 197) died from the lowest risk group. Two of the

156 patients treated with streptokinase suffered a cerebral hemorrhage it is true, one of them dying as a result of this. Otherwise no serious hemorrhagic complications occured.
The study shows that a certain group of patients with an increased risk can benefit from the fibrinolytic therapy. It must be emphasized that only 13.6% of all the patients admitted with a myocardial infarction were treated with streptokinase. No general recommendations can be made from this study either, as to which patients should be given fibrinolytic therapy. The decision has to be made anew in each individual case and is influenced to a considerable extent by the experiences and subjective impressions of the doctor in attendance. A beneficial effect is to be expected in patients with reduced cardiac output in the preshock phase.

Intracoronary Thrombolysis

In the earlier studies the positive effects of the streptokinase therapy were preferentially attributed to the rheological hemodynamic effects. The possible recanalization of the thrombotically occluded coronary artery was considered to be of rather secondary importance. The view was that the recanalization of the coronary artery would take too long to protect the ischemic musculature from destruction. On the other hand this finds its expression in the fact that patients were admitted to the study up to 12 h, often up to 24 h and even up to 72 h after the onset of the infarction. In recent years increasing attention has been paid to the immediate recanalization of the thrombotically occluded coronary artery. A precondition for this is that the patients can receive the therapeutic measures not later than 2–6 h after the onset of the infarction.

Selective Intracoronary Thrombolysis
(under Coronary Angiographic Control)

Selective intracoronary thrombolysis via a catheter of precoronary localization was introduced clinically in 1979. The administration of the streptokinase directly in front of the occlusive thrombus is said to result in a higher concentration and thus in a greater lytic effect on the

thrombus. The patients must be given the fibrinolytic treatment within the first 2 to 3 h up to maximally 6 h after the assumed infarction. It is assumed that if successful thrombolysis takes place within this period of time, the functional capacity of the affected area of myocardium can largely be preserved.

The procedure for selective intracoronary fibrinolysis under coronary angiographic control has been modified several times. An example is given in Fig. 5.

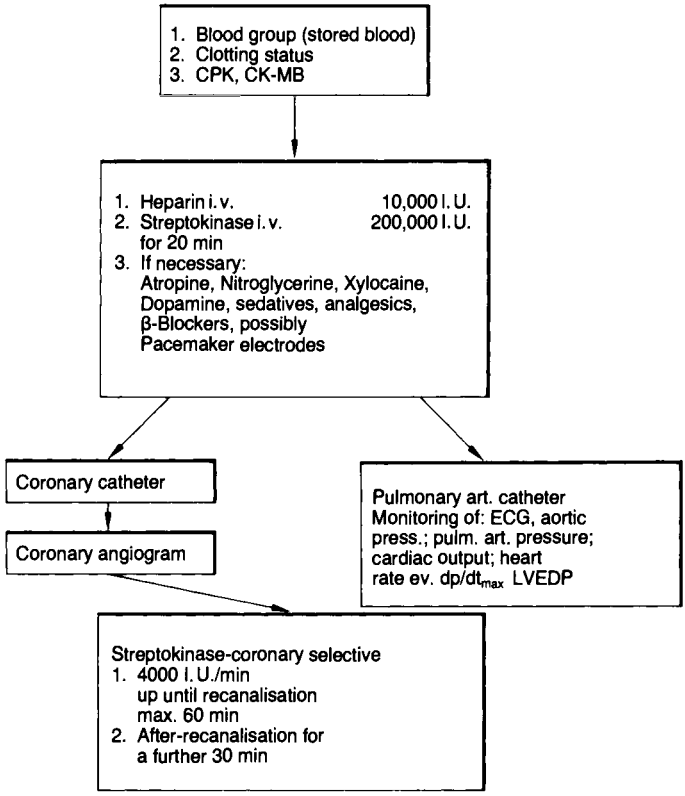

Fig. 5. Diagnostic and therapeutic program for selective coronary streptokinase therapy of acute myocardial infarction (Rutsch, 1982)

Prior to the start of the streptokinase therapy the patients receive 10,000 I.U. of heparin intravenously (as prophylaxis against reactions to streptokinase) 200 mg to 1000 mg of prednisolone, and 0.5 to 1.0 g of acetylsalicylic acid. A preliminary intravenous streptokinase infusion of 200,000 I.U. in 20 min practiced by some groups is said to bridge the therapeutic gap up until the selective administration and to neutralize the antistreptokinase. After visualization of the occluded coronary artery the streptokinase infusion is carried out in front of or into the ostium with 2000 I.U.–4000 I.U. per minute over a period of ca. 30 to maximal 60 min in a total dose of 120,000 I.U. to 240,000 I.U. Control angiographies are performed at intervals of 15–20 min.

After recanalization of the vessel some authors continue to give streptokinase in a dose of 2000 I.U./min for another 30 minutes. After this the anticoagulation is continued for 3–7 days with 800–1200 I.U. heparin/h, with a changeover to oral medication later on. If the vessel still remains occluded after 30–60 min an attempt at transluminal catheter dilatation can be made. The less the age of the thrombus, the shorter the lysis time up until recanalization. The success rate lies between 70 and 93% (Tables 2 and 3). The reobliteration rate after 4 weeks is relatively high. This is understandable since after recanalization of the vessel a residual stenosis of 80–95% remains. In suitable patients a subsequent coronary bypass operation is indicated here. A distinct reduction in the early lethality from 15% in patients whose

Table 2. Results of intracoronary streptokinase therapy, documented by coronary angiography, in acute coronary thrombosis (Schmutzler, 1983).

Centers	No. of patients	Primary recanalization %	Occluded again after 4 weeks %
Boston	30	70	33
Aachen, Göttingen, Berlin, Hamburg	204	84	16
Davis	25	72	17
Heidelberg	93	70	18
Houston	37	73	?
Los Angeles	29	93	?
	418	77%	

Table 3. Recanalization of completely occluded coronary vessels in acute myocardial infarction through intravenous streptokinase therapy. Comparison with intracoronary streptokinase therapy by three authors (Schröder, 1983)

	i.v. Streptokinase recanalization No. patients	Time until recanalization min	i.c. Streptokinase recanalization No. patients	Time up to recanalization min
Schröder et al.	11/21 (52%)	44 ± 19	–	–
Neuhaus et al.	24/38 (63%)	48 ± 13	27/36 (75%)	33 ± 15
Spann et al.	10/20 (50%)[a]	?	–	–
Blunda et al.	8/12 (67%)[a]	54 ± 28	11/13 (85%)[a]	27 ± 14
Huhmann et al.	13/22 (59%)	105 ± 68	20/26 (77%)	55 ± 28
	66/113 (58%)		58/75 (77%)	

[a] Newer figures given

coronary artery remains occluded to 4.7% with recanalized arteries, can be achieved (Fig. 6). Measurable systemic lytic effects can be demonstrated in every case on coagulation analysis. As a rule no dilatation of the vessel lumen could be achieved in patients with unstable angina pectoris and the subtotal occlusion of a coronary artery. The reason for this is that stenotic arteriosclerotic plaques, and older thrombocyte and fibrin thrombi cannot be lysed.

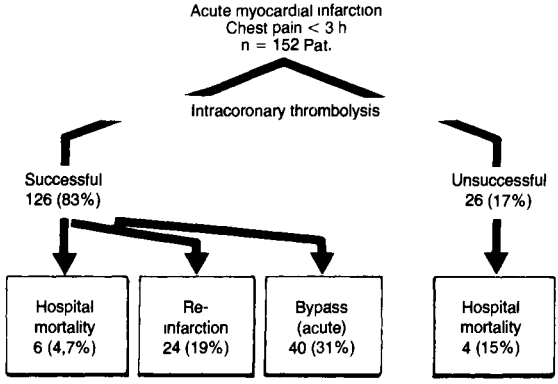

Fig. 6. Clinical course of 152 patients with acute myocardial infarction and intracoronary streptokinase therapy within the first 3 h after the start of the symptoms (Mathey, 1983).

The successful recanalization and an improvement in myocardial function could be documented not only by coronary angiography but also through serial checks on the ECG and CPK, the ejection fraction, the regional wall mobility and thallium scintigraphy. A final assessment of the value and duration of long-term anticoagulation and the inhibition of thrombocyte aggregation is not yet possible – this seems to be absolutely essential however.

It remains an open question as to whether, because of the local bloodflow conditions a higher concentration can really be achieved with intracoronary or directly precoronary administrations of streptokinase directly at the thrombus. In order to take effect at the thrombus the streptokinase must have formed the activator complex with plasminogen localized in the plasma in a very short space of time over the short distance from the tip of the catheter to the thrombus. Another possibility might be that streptokinase diffuses into the thrombus and forms the activator complex there with the coprecipitated plasminogen. This has led to deliberations about whether similar positive results could be achieved with high-dose intravenous infusions of streptokinase (Rentrop et al., 1979, 1982; Rutsch, 1982).

Systemic Fibrinolysis (under Coronary Angiographic Control)

Fibrinolysis with the systemic administration of streptokinase has experienced a revival since 1981. Initially the patients received 500,000 I.U. of streptokinase intravenously given within 30 min one and a half to six hours after the start of the acute symptoms of infarction. 5000 I.U. of heparin, 1 g of acetylsalicylic acid and 250–500 mg of prednisolone had been given intravenously before this. If a coronary vessel was not recanalized after 60 min, patency was achieved by means of transluminal catheter dilatation. This was followed by a one-hour intracoronary infusion of 2000 I.U. of streptokinase/min. The idea behind this procedure is that recanalization of the coronary artery and myocardial protection can also be achieved through sufficiently high-dosed systemic administration of streptokinase, if the treatment commences early enough. Recanalization could be achieved in 65% of cases. The remaining stenoses after 24 h to 3 weeks amounted to between 70 and 90%. By comparison with the angiography after 24 h, after three weeks a further increase in the vessel diameter was

recorded in some cases. After the completion of the fibrinolysis heparin was given according to the thrombin time for 2–3 days. This was followed by anticoagulation with coumarin derivatives. In the patients with successful lysis the maximal plasma concentration for the creatinine phosphokinase was reached on average after 13.5 hours, but, in contrast to this, after 20 h in conventionally treated patients. The increase in the CK was also higher. This was interpreted in the sense of a washout effect from the damaged myocardium. A distinct fibrinolytic effect could be demonstrated in the systemic blood.

The value of this form of therapy has been tested in several studies (Tables 3 and 4). As far as possible the infarction should be less than 3 h old – in any event less than 6 h. After the initial administration of 5000–10,000 I.U. heparin, 0.5–1.0 g acetylsalicylic acid and mostly 500 mg of prednisolone, up to 1.5–1.7 million I.U. streptokinase are infused over maximal 60 min. The rate of recanalization demonstrated by coronary angiography at 46–63% is lower than in patients with intracoronary lysis. The follow-on treatment is carried out as described above.

The findings suggest that a recanalization of the coronary vessel can also be achieved with the systemic administration of streptokinase. Since only a few clinicians have a coronary angiography unit at their disposal, early systemic lysis is an equivalent alternative to the coronary selective procedure (Schröder et al., 1981, 1982, 1983).

Table 4. Recanalization through intravenous streptokinase therapy in acute myocardial infarction. Coronary angiographic control only in some of the cases (Schmutzler, 1983)

Authors	Age of infarct. (h)	Duration lysis (h)	SK dose (units)	No. of patients	Thrombolysis successful
Neuhaus et al.	< 6	1	1.7 million	38	24 (63%)
Schröder et al.	< 6	1	1.5 million	26	16 (62%)
Spann et al.	< 6	1	850000	13	6 (46%)
Genth et al.	< 8	15	ID. 250000 MD. 100000	28	16 (57%)

Thrombolysis with Urokinase

In 80 patients with an infarction less than 12 hours old, after a bolus injection of 2,500 to 10,000 I.U. heparin, intracoronary lysis with urokinase in a dosage of 6,000 I.U./min. was compared with streptokinase lysis in a dosage of 2,000 I.U./min. The thrombolysis lasted for up to two hours. In the urokinase group 60% of the occluded vessels were recanalized, whilst in the streptokinase group the corresponding figure was 57%. Under urokinase the fibrinogen level fell to below 100 mg% in 6% of the patients. Hemorrhages occurred in 11%. The corresponding figures in the streptokinase group were 66% and 29% (Tennant et al., 1984).
With the use of a single bolus injection of 2 million urokinase, administered intravenously to 50 patients with a mean infarction age of 1.8 hours, recanalization of the occluded coronary artery could be achieved in 60% after 1 hour as a mean value. At the same time heparin was given as a continuous infusion (200 I.U./kg and hour). The fibrinogen and plasminogen were lowered for more than 24 hours. No complications were observed (Mathey et al., 1985).

Thrombolysis with Tissue Plasminogen Activator

In 1983 the successful recanalization of occluded coronary vessels was reported for the first time through *t*issue-type *p*lasminogen *a*ctivator (tPA) within 19 to 50 minutes in 6 out of 7 patients with acute myocardial infarction. The "European study group for recombinant tissue-type plasminogen activator" treated 129 patients with acute infarction (less than 6 hours) with tPA or streptokinase intravenously. The mean time from the start of the symptoms up until treatment was 2.9 hours. No angiography was carried out before therapy. The tPA group received an initial bolus injection of 5,000 I.U. heparin followed by 0.75 mg/kg bodyweight tPA for 90 minutes. The streptokinase group initially received 5,000 I.U. heparin, 0.25 g methylprednisolone, 0.5 g acetylsalicylic acid and 1.5 million I.U. streptokinase over 60 minutes. After the end of the infusion 70% of the infarction-related vessels were patent in the tPA-group and 55% in the streptokinase group. As a mean value the fibrinogen level fell to 61% (tPA) and 12% (SK) of the baseline value.

In another study of this research group with 124 patients whose infarction was less than 6 hours old, the success of lysis with 0.75 mg tPA/kg bodyweight – infused over 90 minutes – was investigated by comparison with placebo. After the end of the infusion 61% of the infarction-related vessels were patent in the tPA group and 21% in the placebo group. As a mean value the fibrinogen fell to 22% of the baseline value.

The American TIMI study (*t*hrombolysis *i*n *m*yocardial *i*nfarction) investigated the recanalization of angiographically demonstrated coronary occlusions after myocardial infarction in 214 patients with a mean infarction age of 4.8 hours. The tPA group received 40 mg tPA during the first hour and another 40 mg over the next two hours (total duration of infusion 3 hours). The control group received 1.5 million I. U. streptokinase i. v. over 60 minutes. After 90 minutes 60% of the occluded vessels had been recanalized in the tPA group and 36% in the streptokinase group.

The differences in the favor of tPA were significant in all studies. tPA seems to be at least equivalent to streptokinase, if not superior. tPA also leads to a systemic coagulation defect with a fall in the fibrinogen, the plasminogen, the alpha$_2$-antiplasmin, and to the occurrence of fibrinogen split products. The extent of the coagulation changes was distinctly less marked with tPA – at the dosages selected in the studies – than with streptokinase.

Hemorrhagic complications were also observed with tPA. They probably occurred less frequently than with streptokinase however. The tendency to bleeding is due to the additional medication (heparin), to the systemic fibrinogenolysis which is also present with tPA and to the fact that tPA with a high fibrin affinity lyses the fibrin of freshly closed wounds whatever the localization (e. g. puncture sites).

Thrombolysis with Acyl Enzymes

Some preliminary results have been reported on the thrombolytic therapy of acute myocardial infarction (infarction less than 6 hours old) with the acylated activator complex p-anisoyl-streptokinase-lys-plasminogen (BRL 26921). 5 to 30 mg were administered as a bolus or short-term infusion by both intracoronary and intravenous administration. The maximal therapeutic effect seems to be reached with 25 to 30

mg. After 5 mg of BRL 22921, an angiographically demonstrable reperfusion of 20 to 45% was found, after 30 mg one of 60% to 70% of the occluded vessels. The period of time from the start of therapy up to recanalization was 30 to 60 minutes. A marked systemic lysis effect with a fairly prolonged fall in the fibrinogen to 20% of the baseline value and decreases in the plasminogen and the alpha$_2$-antiplasmin were seen, in particular with a higher dosage. The subsequent heparin therapy therefore first commenced a few hours after the end of the thrombolysis.

Thrombolysis with Prourokinase

A first clinical trial with prourokinase and angiographic controls led to recanalization of the coronary vessels in 5 out of a total of 6 patients with acute myocardial infarction. 40 mg of prourokinase were infused intravenously over 60 minutes. In one patient another 20 mg was then also given by intracoronary administration over 30 minutes. No systemic defect of hemostasis occurred in 5 out of 6 patients (van de Werf, 1986).

Transluminal Coronary Angioplasty

The concomitant antithrombotic treatment with percutaneous catheter dilatation of coronary vessels consists of the initial administration of 1.0–1.5 g of acetylsalicylic acid and 5,000 I.U.–10000 I.U. of heparin given intravenously, The heparin therapy is then changed to oral anticoagulation or else the administration of acetylsalicylic acid is continued alone.

Anticoagulants in Acute Myocardial Infarction

The majority of patients with acute myocardial infarction do not receive any fibrinolytic therapy, either for lack of an indication or the presence of contraindications. The standard therapy consists of the initial administration of heparin followed by therapy with oral anticoagulants or substances which inhibit thrombocyte function. The anti-

coagulant therapy is regularly commenced with heparin in a dosage of between 15,000 I.U. and 30,000 I.U./24 h as a continuous intravenous infusion. After 2–3 days, once the acute phase has been overcome and there is less risk of complications through arrhythmias (ventricular flutter and fibrillation), asystole and cardiogenic shock, an overlapping change is made on to oral anticoagulation with coumarin derivatives. The heparinization is ended when the prothrombin time lies in the therapeutic range or the Quick value has fallen to 15–25%, the Thrombotest to 8–12%. The object of the anticoagulation is to prevent the secondary development of an occlusive coronary artery thrombosis over an existing stenosis, which would be sufficient for the development of an infarction during a phase with arrhythmia or hypotension, to prevent the further spread of an existing coronary artery thrombosis which has induced the infarction, and in particular through a systemically induced plasmatic hypocoagulability to prevent the develop of thrombi in the heart cavities in the region of the infarcted area and also in the venous and arterial vessel system with the danger of embolism.

It is difficult to prove a decrease in the mortality after infarction, through the anticoagulation in particular (Table 5). The causes of death are mainly arrhythmias, cardiac insufficiency, cardiogenic shock and rupture of the heart wall. The phenomena which can be influenced

Table 5. Influence of anticoagulant therapy (heparin and coumarin) in the early phase of myocardial infarction on lethality and thromboembolic complications (Heene, 1981)

Study	No. of patients		Lethality		Thromboembol. complications	
Controls	Contr.	AC therapy	Contr.	AC therapy	Contr.	AC therapy
Brit. Med. Res. Council 1969	715	712	18%	16%	11%	5%
Drapkin & Merskey 1972	391	745	21%	15%	12%	7%
Vet. Adm. Report USA 1973	500	499	10%	11%	13%	4%
Modan et al. 1975	1387	841	27%	8%	–	–
Tonascia et al. 1975	673	483	27%	11%	–	–

by anticoagulation, such as recurrent infarction, and fatal pulmonary and cerebral emboli, make up 0.5–3% in the investigated groups of patients and are of lesser importance in respect of the total lethality. In most studies the period of observation lasts for the hospital phase of 3–6 weeks. With the exception of the studies of Modan et al. (1975) and Tonascia et al. (1975), no significant differences were seen between the anticoagulant and control groups in respect of the lethality. A distinct reduction could be demonstrated in deep vein thromboses of the pelvis/leg, thromboembolic complications and mural thrombi (Tables 5, 6 and 7). An analysis of 32 studies on the other hand, showed a reduction in the lethality during the hospital phase after infarction from 19.6% in the control group to 15.4% in the anticoagulant group. This corresponds to a significant relative reduction of 21% ($p < 0.01$). The positive effect of anticoagulation in the

Table 6. Frequency of deep vein thromboses of the leg (positive radiofibrinogen test) after acute myocardial infarction (hospital phase) with and without anticoagulant therapy (heparin, coumarins) (Heene, 1981)

Authors	No. patients		Frequency of deep leg vein thrombosis	
	Controls	AK ther.	Contr.	AK therapy
Nicolaides et al. 1971	31		38%	5.5%
Handley et al. 1972	24	24	29%	0%
Wray et al. 1973	46	46	21.7%	6.5%
Warlow et al. 1973	64	63	17%	3%
Gallus et al. 1973	40	38	22.5%	2.6%

Table 7. Frequency of mural thromboses in acute myocardial infarction (Deutsch, 1977)

Authors	Placebo	Anticoagulants
Wright	62%	32%
Hilden	58%	24%
Veterans administration study	48.4%	21.7%
Drapkin ♀	45.5%	10%
♂	54.6%	19.2%

avoidance of thromboembolic complications is undisputed. It is not sufficient to use "low-dose" heparin prophylaxis for the avoidance of arterial thromboembolic complications.

Long-Term Anticoagulation After Myocardial Infarction

Opinions still differ as to whether there is any point in giving long-term anticoagulation with coumarius to prevent a repeat infarction and deaths due to repeat infarction. It can be assumed that the number of all recurrent infarctions is lower under anticoagulation. A review of 12 studies from the years 1957 to 1967, which conformed to statistical criteria, showed a reduction in the lethality from 21.8% in the control group to 17% in the anticoagulant group. An analysis of all studies available up to 1979 showed a significant reduction in the repeat infarction rate and in the mortality due to repeat infarctions. A study carried out by the Netherlands Thrombosis Service during a two year observation period in patients aged over 60 years who had already received anticoagulation for at least 6 months (as a mean value 5.9 years), was able to demonstrate a reduction in the reinfarction lethality from 13.4% in the control group, in whom the anticoagulation was interrupted and replaced by placebo, to 7.6% in the group where the anticoagulation was continued ($p = 0.017$). The reinfarction rate could be reduced from 15.9 to 5.7% ($p < 0.001$). Another review of 7 studies from the years 1957 to 1969, which also contained some of the studies in the above-mentioned review, but in which particular attention was paid to the quality of the anticoagulation, resulted in a reduction in the cases of cardiac death per 100 patient years of 41% and in the survived re-infarctions of 61%. The so-called "Sixty-plus" Dutch study mentioned showed a comparable reduction in the two target parameters of 44 and 67% when converted into 100 patient years. The positive result was interpreted in the sense of a reduction in the thrombotic events which are said to be responsible for the progression of the changes in the coronary arteries. A precondition for this is consistent monitoring of the patients which ensures a constant inhibition of coagulation within the therapeutic range. This condition was fulfilled in the optimally organized study of the Dutch Thrombosis Service, but is frequently not guaranteed in many European countries. The positive effect of long-term anticoagulation is adversely affected by this

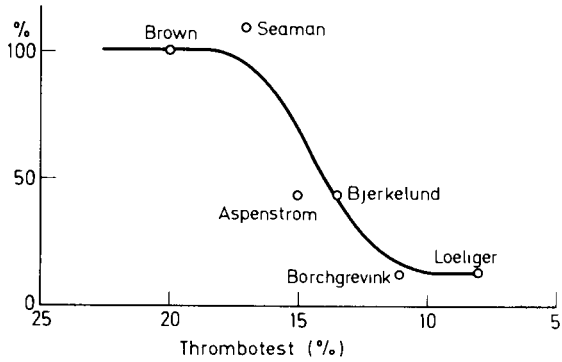

Fig. 7. Relationship between the quality of the anticoagulation and reinfarction rate (Thrombotest: therapeutic range 5–12%). Non anticoagulated patients: reinfarction rate taken as 100% (Loeliger et al., 1967)

and often brought to nothing. At least 75 to 80% of the Quick value checks carried out over a fairly long period of time should lie in the therapeutic range (Fig. 7).

No precise data are available on the length of time for which long-term anticoagulation should be carried out. The period of observation in the studies lay between 1 and 4 years. A beneficial effect is to be expected within at least 2 to 5 years after infarction. In earlier studies male infarction patients aged below 55 years benefited most from the anticoagulation.

Those aged under 45 years have the greatest chance of not experiencing a reinfarction for more than 5 years if long-term anticoagulation is given. Life-long continuous anticoagulation is indicated in:

1. Heart wall aneurysm,
2. Absolute arrhythmia with atrial fibrillation
3. Cardiac insufficiency
4. Persistent angina pectoris
5. Demonstrable generalized degenerative vessel disease
6. State after arterial thrombosis or embolism
7. State after venous thrombosis and/or pulmonary embolism.

The risk of hemorrhage under anticoagulant therapy lies between 3 and 5%. Fatal hemorrhagic complications, especially through

intracerebral bleeding, are said to occur in 0.5–0.8% of the patients. There are no significant differences between the number of cases of death due to cerebral hemorrhage with and without anticoagulant therapy. Attention should be paid to the contraindications, such as hypertension with values over 180 mm Hg systolic and 100 mm Hg diastolic, hemorrhagic diatheses, gastronintestinal ulcers, renal insufficiency, interactions with other drugs (in particular antirheumatics, antiinflammatory drugs), severe liver diseases, malabsorption syndromes, retinopathy with fundus hemorrhages and bacterial endocarditis (Chalmers et al., 1977; Douglas, McNicol 1975; Heene et al., 1977; Heene, 1981; Jaenecke 1982 (R); Jost et al., 1983; Leickert, 1979; Loeliger et al., 1967; Loeliger 1981a, 1981b; de Vries et al., 1980).

Aggregation Inhibitors and Prophylaxis Against Reinfarction

On the assumption that thrombocytes in the arterial vessel system play an essential part in the atherogenesis and thrombogenesis over an arteriosclerotically altered area, drugs which have an effect on platelet function were used as prophylaxis against recurrence of the cardiac infarction. Arrhythmias, which along with other causes can lead to sudden heart death, are said to be induced, inter alia, through platelet emboli in the peripheral coronary vascular system (Fig. 8). The platelet aggregates either become detached from an atheromatous plaque of the coronary artery or else they are platelet aggregates which can be demonstrated in the systemic circulation when there is general hypercoagulability of the blood and which are carried into the coronary circulation.
Acetylsalicylic acid, sulfinpyrazone and dipyridamole are used as drugs to inhibit platelet function. In the studies carried out with the substances mentioned, the end-point was the total mortality, the coronary mortality (sudden heart death, fatal reinfarction) and the incidence of reinfarction. Seven prospective, randomized multicentre studies are available, one of which was carried out with sulfinpyrazone (*A*nturane *R*einfarction *T*rial, ART) and the others with acetylsalicylic acid versus placebo (Table 8). In one study a combination of acetylsalicylic acid and dipyridamole was additionally given (PARIS, *P*ersantin-*A*spirin-*R*einfarction-*S*tudy, 1980). The period of admis-

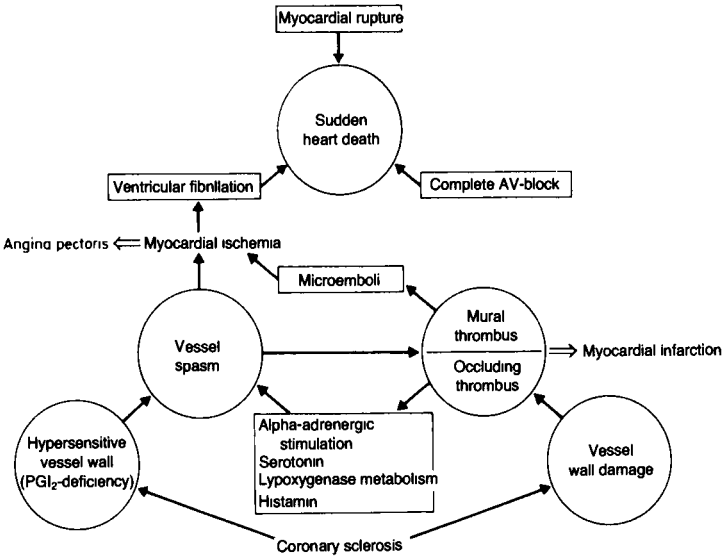

Fig. 8. Possible pathological mechanisms for sudden heart death (Reimers, 1982)

sion to the studies lay between one week (Elwood et al., 1979) and up to 7 years (CDPA study Coronary Drug Project Research Group, 1976) after the infarction event. The mean observation time lay between 16 and 41 months. The dosage of acetylsalicylic acid lay between 1 × 300 mg/day and 3 × 500 mg/day. In the PARIS study besides 3 × 324 mg of acetylsalicylic acid, a combination of 3 × 324 mg acetylsalicylic acid and 3 × 75 mg of dipyridamole was given. In the ART study (1980) the dosage was 4 × 200 mg of sulfinpyrazone. In none of the studies with acetylsalicylic acid was statistical significance reached in respect of the total mortality and the coronary mortality. Apart from the AMIS study (Aspirin Myocardial Infarction Study), however, a distinctly positive trend was seen. The protective action of acetylsalicylic acid was seen more clearly in men than in women. In the sulfinpyrazone study, to which patients were admitted between the 25th and 35th day after infarction, a significant reduction was seen in

Table 8. Long-term treatment with thrombocyte aggregation inhibitors after acute myocardial infarction (Scharrer, 1981)

Authors	No. patients	Sex	Daily dose	Time between infarction and admission to the study	Mean observation period
Elwood et al. 1974	1239	M only	1 × 300 mg ASS	4 wk–14 wk.	24 mon.
CDPA	1529	M only	3 × 324 mg ASS	up to 7 years	22 mon.
Elwood et al. 1979	1682	M + F	3 × 300 mg ASS	up to 1 week	12 mon.
AMIS 1980	4524	M + F	2 × 500 mg ASS	8 wk to 5 years	36 mon.
Breddin et al. 1980	946	M + F	3 × 500 mg ASS	up to 6 weeks	24 mon.
PARIS 1980	2026	M + F	3 × 324 mg ASS or 324 mg ASS + 75 mg dipyridamole	2 mon.–3 yrs.	41 mon.
Anturane Reinfarction Trial 1980	1558	M + F	4 × 200 mg Sulfinpyrazone	25–35 days	16 mon.

Complicance %	Total mortality %	Coronary mortality %	Coronary mortality & non fatal reinfarct. %	Non fatal reinfarct %
–	−24.0			
80	−30.0	−27.0	−21.0	−12.0
70	−17.3	−22.0	−28.0	−34.0
90	+11.0		− 5.0	−22.0
80	−17.3	−42.3	−36.0	−30.0
70	−18.0	−21.0	−24.0	−30.0
	−16.0	−24.0	−25.0	−20.0
80	−29.0	−31.0		

the cases of sudden heart death by comparison with the placebo group within the 2nd–7th month after infarction. The incidence of reinfarction was not reduced. This result was explained by saying that besides the inhibition of thrombocyte function, sulfinpyrazone possibly has an antiarrhythmic action through a cytoprotective effect.

Three phases could be distinguished in the post-infarction period (Fig. 9). The first recovery phase extends roughly up to the 30th day and corresponds to the hospital phase. The mortality amounts to about 15–20%. The causes of death are mainly electrical instability and pump failure of the heart. The early post recovery phase consists of the next 6 months. With decreasing frequency another 6 to 10% of the patients die. The primary cause of death is sudden heart death with obviously persisting electrical instability. In the late post recovery phase after the 7th month 3–4% of the patients die annually. None of the causes of death, reinfarction, sudden heart death and progressive heart failure, predominates. In contrast to most of the other studies, it was precisely in the early post recovery phase that the aggregation inhibitor sulfinpyrazone was given. On the basis of the findings available it can be said that the thrombocyte aggregation inhibitors are mainly effective in the early phase up to one year after myocardial

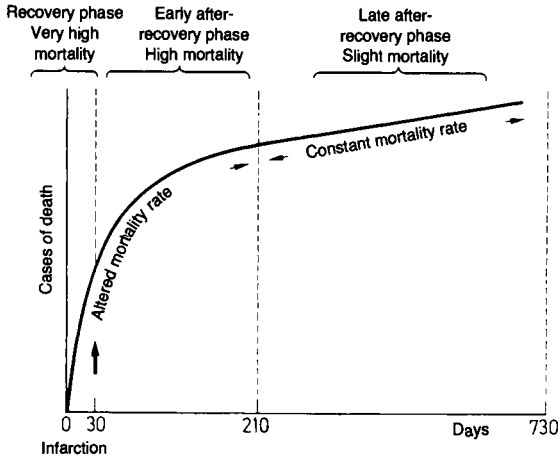

Fig. 9. Relative cumulative mortality after acute myocardial infarction (Sherry, 1982a, 1982b).

infarction. During this period they seem to be equivalent to anticoagulation with coumarin derivatives. The so-called EPSIM study (*E*nquête de *P*revention *S*econdaire de 1'*I*nfarctus du *M*yocarde) (1982), in which 3 × 0.5 g acetylsalicylic acid per day were compared with oral anticoagulants, did not result in any significant difference in respect of the primary end-point, the total mortality. There was a positive tendency in the favor of the anticoagulation. The patients were admitted to the study a mean of 11.4 days after infarction and were kept under observation for 6 to 59 months (mean 29 months). At the present time no adequate data are available on the value of long-term prophylaxis with aggregation inhibitors. The following therapeutic recommendation can be made:

1. 3 × 500 mg acetylsalicylic acid;
2. 3 × 324 mg acetylsalicylic acid combined with 3 × 75 mg dipyridamole;
3. 4 × 200 mg sulfinpyrazone.

Only few data are available on a more favorable effect of a lower dosage of acetylsalicylic acid, such as might be assumed on the basis of biochemical and experimental investigations.

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X. Fibrinolytic and Long-Term – Therapy in the Arterial Vessel System

Fibrinolytic Therapy of Occlusions and Stenoses of Extremity Arteries

The majority of arterial stenoses and occlusions occur in the terminal aorta and the arteries of the leg. The larger therapeutic studies carried out so far relate to this vessel area. The current concepts of therapy are presented in Tables 1 and 2.

Table 1. Concept of therapy in peripheral arterial occlusive diseases (PTR: percutaneous transluminal catheter recanalization) (Schoop, 1981)

1. Acute arterial occlusion	
a) With severe ischemia:	OP reconstruction
if not possible:	Thrombolysis, poss. local
b) Without threatened necrosis:	
Embolism:	OP reconstruction
	Poss. thrombolysis
Thrombosis:	Thrombolysis, poss. OP
c) With good prognosis:	Anticoagulation
2. Subacute arterial occlusion	
a) Leg arteries	
(Mostly fem./pop. art.)	
< 4–6 weeks:	Thrombolysis, poss. local
> 4–6 weeks:	PTR (poss. with thrombolysis)
b) Pelvic arteries	
Weeks – months:	Thrombolysis, poss. OP

Table 1. (Continued)

3. Chronic arterial occlusion	
Stage II:	Training
If inadequate improvement:	
a) Pelvic arteries	
High-grade stenoses:	PTR, lysis
Occlusions:	OP reconstruction (if no major risk)
b) Arteries of leg	
High-grade stenoses:	PTR
Occlusions	
Short section:	PTR
Long section:	OP reconstruction
Stage III:	Recanalization (OP, PTR, thrombolysis)
If recanalization not possible or too risky:	Bedrest, improvement in hemorheological state through infusions and/or reduction in fibrinogen
Stage IV	
a) Good compensation (systolic malleolar arterial pressure > 60 mm Hg):	Recanalization through PTR or OP
If not possible or too risky:	Local treatment, initially bedrest, poss. improvement in rheological state
b) Poor compensation (systolic malleolar artery arterial pressure < 50 mm Hg):	Recanalization through OP or PTR
If not possible:	After failure of all conservative possibilities (see above) amputation

Acute Arterial Occlusion

Acute thrombotic and embolic occlusions of the arteries of the extremities are primarily an indication for vascular surgery, especially if a complete ischemia syndrome is present. Primary lysis therapy is probably indicated in a maximum 5–10% of acute thrombotic occlusions. Fibrinolytic therapy is indicated if in the incomplete ischemia syndrome there is sufficient time for this without endangering the

Table 2. Suggested therapy in subacute and chronic peripheral circulatory disorders (Denck, Fischer, 1981)

	Primary attempt at thrombolysis	Transluminal dilatation	Primary vessel reconstruction
Aorta + iliac vessel	< 2 years Short occlusion II (III)	Stenosis (II) III IV	(Stenosis) Occlusion 2 years II III IV
Femoral + politeal vessel	< 8 weeks Stenosis Short occlusion (II)	Stenosis Short occlusion (II) III IV	(Stenosis) Occlusion (run off) > 8 weeks II III IV
Occlusion only a few days old with poor run off	+		
Recurrent occlusion after reconstructive vascular surgery	+++ 4 weeks postoperative		

limb, if the occlusion cannot be eliminated or only with difficulty by surgery on account of its peripheral localization, or if there are general contraindications to anesthesia and/or the surgical operation. Emboli can be lysed more easily than thromboses and have a high tendency to spontaneous fibrinolysis. It is often sufficient just to reduce the size of the thrombus in order to restore adequate perfusion of the extremity through the exposure of collateral branches. In individual cases through primary fibrinolysis, preconditions can be created which make possible a percutaneous transluminal recanalization by means of catheter dilatation (angioplasty) of the remaining vessel occlusion. If an acute reocclusion develops after catheter dilatation, fibrinolytic treatment can be tried prior to any surgical operation which may become necessary, this being successful in roughly half of such cases. In acute occlusions the success of thrombolysis seems to be largely independent of the localization of the occlusion. In acute arterial thromboses complete recanalization can be achieved in about one third of cases and partial recanalization in a maximum of another

quarter of the cases. Arterial emboli can be completely eliminated in about half of the patients and partially eliminated in up to another third.
The necessary duration of the lysis increases with the interval of time between the acute thromboembolic event and the start of therapy. In the first 5 days after the occurrence of the clinical symptoms, a complete or partial success rate of 50% or more can be reckoned with, if the treatment is indicated. The dosage of the fibrinolytic agent is generally 250,000 I.U. initially and 100,000 I.U. per hour for 1–3 days.

Subacute and Chronic Arterial Occlusion

When occlusions have persisted for some time the success of fibrinolytic treatment depends on several factors: the localization of the occlusion, the length of the occlusion and the duration of the occlusion or symptoms. The greater the diameter of the occluded vessel, the more often a complete or partial recanalization will be possible. If the vessel diameter is less than 6 mm, the possibility of lysing the occluding thrombus is distinctly reduced. The same is true for occlusions of more than 10 cm in extent. Occlusions over longer sections have less of a chance of recanalization. Generally one can assume that thrombotic material which can be lysed is still present 4–6 weeks after the occlusion irrespective of the level at which it is localized.
To increase the success rates numerous variants of the administration of streptokinase have been used, in accordance with the experimental and theoretical concepts described in the previous sections, and these will be dealt with in the following. The majority of investigators initially infuse 250,000 I.U. streptokinase within 20 min and continue the lysis with 100,000 I.U./h. Recanalization of the vessel can be expected after 1–3 days. Lysis is generally not carried out for longer than 5 days. In some cases it is useful to continue the fibrinolysis with urokinase. 800–1500 I.U. heparin/h are additionally infused beginning 1–2 days after the start of the lysis. The amount and start of the heparin administration depend on the lytic effect demonstrated in the systemic blood. After the end of the fibrinolysis the administration of heparin is continued until the coumarin therapy which follows offers adequate anticoagulatory protection.

Occlusions of lower leg arteries do not respond adequately, or only in exceptional cases, to lysis. Fibrinolysis of femoropopliteal occlusions seems to be meaningful up to 6 weeks after obliteration or the start of the symptoms. Under optimal conditions and with very strict indications for treatment, recanalization of femoral arteries could be achieved within 2 weeks after occlusion in 75%, within 2 to 6 weeks in 57% and within 6 weeks up to 3 months in 38% of cases. Obliterations of the iliac arteries (common iliac artery, external iliac artery or both arteries) could be lysed in all cases when the occlusion had lasted for up to 2 weeks, in 66% for up to 6 weeks, and in 31% still for up to 6 months. As a rule fibrinolytic treatment seems justifiable up to 3 months after occlusion. In cases of occlusion of the terminal aorta with and without additional bilateral iliac occlusion, recanalization could still be achieved after 6 months in 23% of the patients. In individual cases occlusions of the aorta can still be lysed up to 2 years after their development.

It will in no way be possible to achieve such results as a rule. Table 3 shows a synopsis of a multicenter study on fibrinolytic treatment of occlusions of the extremities and stenoses using streptokinase, independently of the age of the obliteration.

Arterial Stenoses

There are greater chances of eliminating or dilating stenoses by thrombolysis than occlusions (Table 3). The success rate is between 50 and 65% in the region of the aorta irrespective of the age of the stenosis,

Table 3. Results of a multicenter study on streptokinase therapy in chronic arterial occlusive disease. Recanalization in per cent (Heinrich, 1975a, 1975b; from Schöndorf, Lasch 1981)

	Occlusion 172/619 (27.8%)	Stenosis 207/414 (50%)
Aorta Iliac artery Femoral artery	19–43%	50–65%
Popliteal artery Lower leg arteries	4–20%	14–20%

and in the femoral, popliteal and more peripheral arteries still lies between 14 and 20%. Stenoses of particularly short sections of ½ to 3 cm in length, which show an irregular, crumbly surface on the angiographic picture, are accessible to fibrinolytic therapy. As regards the differential indications for surgery, several successive stenoses of short sections are suitable for fibrinolytic therapy. Recently thrombosed arterial aneurysms, which are often found in the popliteal region, are a rewarding indication for fibrinolytic therapy. They do not make a subsequent vascular surgical operation unnecessary however, since reocclusions are to be expected.

Late Results of Fibrinolytic Therapy

After successful fibrinolytic therapy a pathologically altered vessel wall often with residual stenosis of the lumen remains in the recanalized vessel area. There is the danger of reobliteration, especially if the run off of blood is impaired through stenoses and obliterations in the distal vessel regions. If reobliteration does not occur in the first days after successful recanalization, it can be expected that the vessel will remain patent for a relatively long time. Recanalizations in the aortic and iliac regions in particular have a good prognosis. Surprisingly enough successfully lysed stenoses rethrombose more rapidly than occlusions. A reocclusion rate of 21% can occur within 6 years, with up to 14% reobliterations in the region of the iliac artery, and up to 50% in the region of the femoral artery. Consistent anticoagulation seems to be meaningful in every case. This particularly applies after the recanalization of peripheral sections of arteries. Fairly large studies are not available. A final assessment of the prophylactic value of aggregation inhibitors is not possible at the present time.

Variations on Fibrinolytic Therapy

Mostly fibrinolysis is carried out using the so-called standard lysis. In order to increase the success rates and to reduce the risk of hemorrhage, alternative fibrinolytic schedules have been suggested. In the "adjusted lysis" the initial dose is determined, in dependence on the antistreptokinase titer, according to the so-called "titrated initial

dose". Then 2/3 of the initial dose is given hourly, but as a rule not less than 40,000 I.U. of streptokinase/h. With ultra-high streptokinase dosages 1.5 million I.U./h are infused over 6 hours. In order to have adequate amounts of plasminogen available, the streptokinase infusion was interrupted for 24 h and then it was either continued for another 6 h or else 250,000 I.U. streptokinase were administered daily within 30 min. With the idea of achieving the greatest possible lytic effect on and in the thrombus and of having an adequate amount of activator complex available, variations were introduced: plasminogen was infused first of all at 12 hour intervals within 30 min, followed by a 30 minute infusion of streptokinase or, conversely, streptokinase was given first and then the plasminogen. Other variations are fibrinolysis with the infusion of preformed streptokinase/plasminogen activator complex, and with low-dosed streptokinase at 10,000–30,000 I.U./h.

There have been few reports on the fibrinolysis of chronic arterial occlusions with urokinase. The systemic infusion of amounts of 40,000–50,000 I.U./h has apparently not led to any satisfactory results; higher doses of 100,000 I.U./h are more effective. The fibrinolytic treatment was combined with the catheter-dilatation procedure. Following primary fibrinolysis residual occlusions or stenoses were dilated. The reversed procedure, fibrinolytic therapy following upon transluminal catheter dilatation, has similarly been used. The streptokinase or urokinase were infused in a low dosage through the dilatation catheter left in situ, directly into the region of the thrombosis. The results seem to be promising.

Further Indications for the Use of Fibrinolytic Therapy

Special indications for fibrinolytic therapy are recently thrombosed Scribner shunts and Brescia-Cimino shunts of hemodialysis patients. Individual case reports are available on fibrinolysis carried out for occlusion of the extra- and intracranial circulation of the carotid artery, the basilar artery and of an aorto coronary bypass.

In patients with recurrent occlusions after arterial vascular surgical reconstruction of the aortoiliac and femoropopliteal vessels, complete and partial recanalizations can be achieved through fibrinolysis.

Long-Term Therapy with Anticoagulants and Aggregation Inhibitors

Chronic Arterial Occlusive Disease

Chronic arterial occlusive disease of the lower extremities is often accompanied by obstructions to the circulation in other parts of the arterial vessel system (coronary artery disease, carotid stenosis, apoplexy). Once obstructed arterial flow has been demonstrated clinically or by angiography, there is rapid progression of the vessel changes. In about half of the patients a stenosis or occlusion of the femoral artery is present, either isolated or in combination with changes in the vessel segment before and/or after it. In patients with arterial occlusive disease of the extremities with femoral arteries still clinically patent, an occlusion occurred in 30% within an observation period of 4½ years. For femoral arteries over which a circulatory murmur could be heard on auscultation, but in which no hemodynamic effect could yet be demonstrated, the occlusion rate was 50%, and for femoral arteries with a stenosis affecting the hemodynamics it was even 80%.

As a rule progression of the obliterating process develops proximally to an existing occlusion. In patients with occlusion of the femoral artery but a still patent pelvic circulation, the occlusion rate of the iliac artery was 5%, if circulatory murmurs were already present at the first investigation the figure was 10%, and if an iliac stenosis could be demonstrated, the occlusion rate lay at 33% within the observation period of 4½ years.

Efforts made to stop or slow down the progression of the arterial occlusive disease through anticoagulants and in recent years through aggregation inhibitors of platelets, show positive trends. The studies carried out, which often do not fulfil statistical requirements, generally cover an observation period of 1½ to 4½ years.

Within a period of 3½ years, the amputation rate could be reduced to about 20% in the patients treated with anticoagulants by comparison with the control group. The mortality due to vascular complications of any kind was 50% lower. New occlusions of the arteries of the extremities developed in 0.8% of cases under anticoagulation, and in 2.8% of cases in the control group. Documented through angiographies, the development of fresh stenoses and the progression of pre-existing stenoses could not be significantly reduced by comparison

with a control group in patients receiving anticoagulation with coumarin derivatives within an observation period of 3.7 years. The development of new occlusions and the prolongation of pre-existing occlusions was significantly less however in the anticoagulant group. Fibrin thrombi are involved in the transition of arterial stenoses into occlusions at least, and these can be prevented or their formation delayed through oral anticoagulation. Here also the quality of the anticoagulation is decisive.

In recent years the effects of aggregation inhibitors on the progression of arterial occlusive disease have been investigated and compared with placebo and also with some anticoagulants. To date only acetylsalicylic acid has been used in a dosage of 1.5 g (3×0.5 g/day) and a combination of acetylsalicylic acid 990 mg daily combined with 225 mg dipyridamole. The periods of observation amounted to 1–3 years. The patient groups comprised 50 to 600 persons. Using noninvasive methods of investigation a distinctly positive trend could be demonstrated in favor of the treatment groups in respect of the progression of a stenosis and the development of new occlusions. If in comparison a group was treated with anticoagulants, then the positive effect was of approximately in the same order of magnitude.

Adequate reports are not available on the therapeutic and prophylactic action – postulated on the basis of theoretical considerations and biochemical findings – of a low dose of acetylsalicylic acid of 50–100 mg per day alone or in combination with dipyridamole in a dose of 225 mg per day or more. Long-term therapy with anticoagulants and inhibitors of platelet aggregation has an obvious positive effect. At the present time it cannot be decided which drug should be given preference. In any case one is dealing with a treatment which entails risks. It is not easy to judge whether the often not completely convincing therapeutic results justify the use of the drugs, taking the hemorrhagic complications into account, and this has to be decided by the physician in each individual case. General use is not to be recommended. The decision to give oral anticoagulants is made easier if the patient is reliable and there are adequate monitoring facilities. If at the same time there is an underlying cardiac insufficiency, atrial fibrillation with an enlarged left atrium or some other disease in which anticoagulation is indicated, the decision can be made without difficulty. Laboratory checks are not necessary with the use of aggregation inhibitors. Their use is limited by the gastrointestinal intolerance.

Percutaneous Recanalization Using the Catheter Method

Catheter dilatation is indicated for stenoses and occlusions of short sections in the region of the iliac artery, the femoral artery and the popliteal artery. During the mechanical dilatation thrombus material is compressed at the vessel wall. Vessel wall lesions and intimal tears occur. This creates a highly thrombogenic surface. The expected early reocclusions within the first 24 hours after the procedure and also the late reobliterations in the course of the first 1 to 2 weeks are relatively high. Here dilatations in the region of the iliac artery have a greater chance of remaining patent because of the better circulation conditions than, recanalizations in the region of the femoral artery. Immediately after the procedure an initial dose of 5000 I. U. heparin is given and is continued with 20,000 I. U. to 30,000 I. U. per day. The anticoagulation with heparin can also commence during the operation. The heparin therapy is stopped as soon as the oral anticoagulation with coumarin derivatives has reached the therapeutic range. The primary success rate in transluminal recanalization lies between 80 to 90%. On the assumption that the thrombocytes play a dominant role in the rethrombosing process, the use of aggregation inhibitors was suggested. 1 to 2 days before the operation treatment was commenced with 3×0.5 g acetylsalicylic acid, 0.33 g acetylsalicylic acid or with a combination of 3×0.33 g acetylsalicylic acid and 75 mg of dipyridamole and the prophylaxis against reobliteration was continued after the procedure. Additional heparin therapy in the first 24 to 48 hours after the operation can perhaps further reduce the incidence of early reocclusions. Under anticoagulants rethrombosis occurred within 7 to 14 days in 21 to 31%. Under anticoagulants combined with acetylsalicylic acid the rethrombosis rate within 14 days was 6.6%, under acetylsalicylic acid alone it was up to 30%, and 16% with acetylsalicylic acid in combination with dipyramidole. Long-term treatment with aggregation inhibitors, which commences before the operation and is combined with heparin during and for 24 to 48 hours after it, is to be recommended.

Vascular Surgery

In reconstructive vascular surgery regardless of the operation procedure and irrespective of the localization of the arterial occlusion,

perioperative anticoagulation with heparin is indicated in every case. In thromboendarteriectomy and bypass operations it is a question of preventing early occlusions in the first days during the phase of perioperative systemic hypercoagulability, and the new development of stenoses and obliterations in arteriosclerotically altered vessel areas outside of the operation area, and of avoiding the occurrence of postoperative venous thromboses. As a rule the dosage amounts to 5000 I. U. of heparin intraoperatively and depending on the prolongation of the thrombin time (2–3 times the norm) 20,000 I. U. to 30,000 I. U. per 24 h over the next few days. The incidence of early and late occlusions depends on the age of the patient, the surgical technique used, the nature of the vessel wall in the operated vessel section, the stage of the arterial occlusive disease and the peripheral run off conditions. Patients aged over 60 years who additionally suffer from a cardiac insufficiency tend to have recurrent occlusions more often than younger patients without any concomitant diseases with an increased risk of thrombosis. Predisposing factors for arterial occlusive diseases such as diabetes mellitus and hyperuricemia etc., favor reocclusion. Independently of any anticoagulant therapy, thromboendarteriectomy and prosthetic operations in the aortoiliac region show the best results after a 5 to 10 year observation period, followed by aortofemoral bypass operations, aortofemoral desobliterations, femoropopliteal vein bypass, femoropopliteal synthetic prostheses and femoropopliteal desobliteration. The re-occlusion rate after 10 years is 60% for femoropopliteal bypass and 85% after femoropopliteal thrombo-endarteriectomy. Table 4 gives an overview of the frequency of re-occlusion up to 2 years after vascular surgery.

The investigations of Bollinger et al. (1981a, b) provide the first indications for differential prophylaxis after vascular surgical procedures in the femoropopliteal region. Within an observation period of 2 years after thromboendarteriectomy with long-term anticoagulant prophylaxis reobliteration occurred in 42% of the patients, but in only 20% under acetylsalicylic acid plus dipyridamole. After the implantation of a vein bypass reocclusions occurred in 17% under anticoagulants and in 32% under acetylsalicylic acid plus dipyridamole. Thus the results after thromboendarteriectomy were just as good under aggregation inhibitors as for the vein bypass under anticoagulants. No conclusive studies are available on the value of anticoagulant therapy with synthetic prostheses.

Table 4. Percentage of reocclusions after vascular surgery (PLB: placebo; ASS: acetylsalicylic acid; AK: anticoagulation; TEA: thromboendarteriectomy) (From Schöndorf, 1981)

Localisation	n Pat	PLB	ASS	AK	Observation (Months)	Type of OP	Authors
Aortoiliac	265	7%		6%	24	?	Denck et al. 1981
	98		4%	2%	6		Waibel 1976
Femoro-poplietal	412	18%	12%	9%	24	?	Denck et al. 1981
	428	22%	11%		12	TEA 80%	Ehresmann et al. 1977 (37% aortoiliac OP)
	122		20%	49%	24	TEA	Schneider et al. 1979
	91		35%	13%	24	Veinbypass	prospect. randomized
	247	32%		26%	?	TEA	Saggau 1977
	38	27%		19%		Veinbypass	
	28		33%	12%	6	?	Waibel 1976
	180		20%	42%	24	TEA	Bollinger et al. 1981
	90		32%	17%	24	Veinbypass	

To sum up, anticoagulation with coumarin derivatives can be recommended for a period of 1 to 2 years after operations in the aortoiliac region. Prolonged anticoagulation depends on possible concomitant diseases. Continuous anticoagulation seems to be indicated in every case after operations in the femoropopliteal region, especially when there are poor run off conditions and concomitant diseases with an increased risk of thrombosis. The use of inhibitors of platelet aggregation is particularly justified after thromboendarteriectomies.

Heart Valve Defects and Heart Valve Replacement

Mitral valve defects have an embolism frequency of 15%. Patients with simultaneous atrial fibrillation and a dilated left atrium are particularly at risk. In aortic valve defects an arterial embolism occurs in ca. 5% of cases. Patients with recurrent embolism are often found to have a shortened platelet survival time. About half of the emboli are transported into the cerebral vessel system.

In mitral valve defects due to rheumatism in particular, with atrial fibrillation and a dilated left atrium, continuous anticoagulation has been shown to have a positive effect. Aggregation inhibitors are not sufficiently effective (cf. Chap. VIII).

In cases with artificial heart valves one has to distinguish between emboli which originate from thrombi on the valve prosthesis and thrombosis of the heart valves which can lead to dysfunction and heart failure.

Of the emboli which originate from implanted valves, 66% are carried into the cerebral arterial vessel system. 10% of these emboli take a fatal course. 25% are transported into the coronary vessel system and result in death in about one third of cases. The remaining of emboli mostly pass to the mesenteric arteries, the retinal vessels and the arteries of the arm (3% each). The frequency of embolism depends on the position and type of the valve and the number of implanted heart valves. Mitral valves have the highest risk of embolism. This is even higher than in combined valve replacement. It is lowest for aortic valves (Table 5).

In the course of the past few years the frequency of embolism has been distinctly reduced to 1.2 to 6% per year through anticoagulation with coumarin derivatives. Emboli are seen most often with the older Starr-

Table 5. Frequency of arterial embolism in patients with Björk-Shiley valve in dependence on its position; all of the patients received anticoagulant therapy (Björk and Henze, 1979; from Lechner et al., 1981)

	Embolism/100 patient years
Aorta	0.7
Mitral valve	4.2
Aorta + mitral valve	2.2
Mitral + tricuspid valve	1.5

Edwards valves. Emboli occur with decreasing frequency with plastic-coated Starr-Edwards valves and with the lowest frequency for porcine bioprostheses.

The highest incidence of embolism is found as a consequence of the systemic hypercoagulability during the perioperative phase and the weeks following this. As a rule long-term anticoagulation is dispensed with for the bioprostheses, but anticoagulation is recommended post-operatively for bioprostheses in the aortic position during the first 6 weeks and in the mitral position during the first 12 weeks after the surgical operation. Long-term anticoagulation with bioprostheses is necessary for intraatrial thrombi, marked enlargement of the atria with atrial fibrillation, severe arteriosclerotic changes and postoperative embolism. It is necessary in about 9% of the aortic valves, 32% of the mitral valves and 33% of the aortic and mitral valves. The frequency of embolism depends on the quality of the anticoagulation (Table 6).

The administration of inhibitors of thrombocyte aggregation alone (acetylsalicylic acid, dipyridamole) is not sufficient. The combination of the aggregation inhibitors mentioned has a positive effect, as does

Table 6. Frequency of arterial embolism in dependence on the quality of the anticoagulant therapy (Lechner et al., 1981)

% of time in the therapeutic range	Emboli/100 patient years	
	Mitral valve	Aorta
> 90%	3.24	0
< 90%	15.4	2.2

Table 7. Thrombotic obstructions of the Björl-Shiley valve under anticoagulant therapy per 100 patient years (Björk and Henze, 1979, from Lechner et al., 1981)

	Frequency/100 patient years
Aorta	0.3*
Mitral valve	1.3
Tricuspid valve	2.3

* Without anticoagulants 8.1%

the combination of oral anticoagulants and dipyridamole. The combination of anticoagulants with acetylsalicyclic acid is associated with a relatively high risk of bleeding and is not to be recommended.
Thrombotic obstructions also occur under anticoagulants and are most frequent with tricuspid valve prostheses, followed by valve replacement of the mitral valve and the aorta (Table 7).
In patients with artificial heart valves a pregnancy should be carried to term only if this is of the degree of severity NYHA I and II (**N**ew **Y**ork **H**eart **A**ssociation). Anticoagulation with coumarin derivatives in the first trimester entails the danger of so-called warfarin embryopathy for the child. The incidence of abortions in the first trimester is very high at 60% in women receiving coumarins because of artificial heart valves. In the last trimester and during the birth the risk of hemorrhage represents a danger to both the mother and the child. Anticoagulation with heparin is to be recommended in the first and last trimester. The administration in a dose of 2×10,000 I.U. to 2×15,000 I.U. subcutaneously can be carried out by the pregnant woman herself. The thrombin time should still be somewhat prolonged 1–2 h before the next injection. About 2 weeks before the date of delivery a changeover is made on to intravenous administration of heparin. There are no objections to coumarins in the middle trimester.

Endocarditis

The general view is that anticoagulation is not indicated in uncomplicated infectious endocarditis of natural heart valves and of biopro-

stheses. The risk, in particular of cerebral hemorrhagic complications, is considered to be relatively high. If systemic thromboemboli occur, anticoagulation is indicated regardless of the nature of the heart valve. Concomitant atrial fibrillation, intracardiac thrombi and thrombotic valve deposits are criteria which argue in favor of antithrombotic therapy. If an endocarditis develops in a patient with artificial heart valves receiving antithrombotic therapy, this should be continued.

Aortocoronary Vein Bypass

During the first postoperative months occlusions of the bypass occur in 5 to 15% of cases, and here the systemic hypercoagulability during the postoperative phase undoubtedly plays a decisive part. The rate of occlusion is influenced by the experience of the surgeon, the localization of the vessel sections which are to be bypassed and the vessel changes distal to the anastomosis. During an observation period of between 6 and 40 months, it was demonstrated on angiography that 72% of all transplants remained patent after the administration of placebo, 84% with the administration of oral anticoagulants and 80% with acetylsalicylic acid. 3 to 6 months after the operation it could be shown by angiographic controls that there were 92% patent transplants under acetylsalicylic acid (1.5 g) plus dipyridamole (100 mg) by comparison with 78% in the placebo group. It was also demonstrated, however, that anticoagulant prophylaxis against occlusion was ineffective.

The benefits of long-term prophylaxis with anticoagulants or aggregation inhibitors do not seem to have been adequately confirmed at the present time. Prophylaxis is undoubtedly justified during the first postoperative months.

It can be recommended that the antithrombotic therapy should start 2 days before the operation with 375–450 mg dipyridamole per day, and should be continued from the day of operation onwards with the combination of 1.0 g acetylsalicylic acid and 225 mg of dipyridamole per day.

Unstable Angina Pectoris

With 325 mg acetylsalicylic acid per day the nonfatal cardiac infarctions could be reduced within an observation period of 12 weeks from 6.9% to 3.4% and the fatal cases from 3.3% to 1.6%, i. e. significantly by about 50% in each case. With 4×325 mg acetylsalicylic acid per day the frequency of cases of cardiac death and of nonfatal cardiac infarctions could be significantly reduced from 13% to 6% within an observation period of 19 months. It is recommended that 325 or 500 mg of acetylsalicylic acid should be given per day up to the cardiac surgical operation or for at least two years. Aggregation inhibitors are to be preferred to oral anticoagulants.

Arteriovenous Hemodialysis Shunts

In uremic patients there is an increased tendency to bleeding, which is mainly due to a disorder of platelet function in the context of the underlying disease. Nevertheless, after Cimino and Scribner shunts thromboses which occlude the shunt occur postoperatively in 9 to 15% of cases. Late thromboses are given as about 22%. The functional longevity of a shunt is about 30 months. By comparison with a control group the frequency of occlusion could be significantly reduced through the low-dose administration of acetylsalicylic acid 1 g every 2nd day or 160 mg per day. A reduction in the shunt thromboses was also seen under sulfinpyrazone in a dosage of 3×200 mg. There was no increased incidence of gastrointestinal bleeding. A reduction in the shunt-thromboses could also be achieved with anticoagulants. A higher incidence of hemorrhagic complications has to be reckoned with. In patients with a tendency to frequent shunt thromboses the administration of coumarin derivatives or of acetylsalicylic acid is indicated, in some cases combined with dipyridamole. It is not certain whether the administration of dipyridamole alone is sufficient. It should be taken into account that non-protein-bound coumarins are dialyzable.

Hemodialysis and Hemofiltration

The anticoagulation with heparin which is required must be individually adapted in accordance with the clotting time, the partial thromboplastin time or the thrombin time. The anticoagulation can be carried out continuously, intermittently or regionally. With continuous anticoagulation the initial dose amounts to between 2,500 and 5,000 (up to 7,500) I. U., the maintenance dose to between 500 and 2,500 I. U./hour. With plasma separation the dose lies in the same order of magnitude. A heparin-sparing effect can be achieved through the additional administration of prostacyclin (ca. 5 ng/kg bodyweight and minute), this presumably being mediated via the inhibition of procoagulatory activities of the thrombocytes.
Low molecular weight heparin has been successfully used for anticoagulation in hemodialysis and hemofiltration. In patients with a low risk of hemorrhage, an initial dose of 30 to 35 (up to 40) I. U. anti Xa/kg bodyweight was given as a bolus and then 10 to 15 I. U. anti Xa/kg and hour. The anti Xa values in the plasma were to lie at 0.5 to 1.0 I. U./ml. In patients at risk from hemorrhage an initial dose of 5–10 I. U. anti Xa/kg bodyweight and a maintenance dose of 4–5 I. U. anti Xa/kg and hour are recommended, with a plasma level of 0.2 to 0.3 (up to 0.4) I. U. anti Xa/ml being aimed at.

Catheter Procedures in the Arterial System

Thombosed vessels occur in 0.3 to 30% of the patients after catheter procedures with open arteriotomy. After percutaneous catheter introduction the incidence of thrombotic complications lies at between 1.7 and 3.5%. Under oral anticoagulants arterial thromboemboli could be reduced to 5.7% by comparison with 18% in the placebo group. No positive effect could be demonstrated under acetylsalicylic acid. A distinct reduction was recorded however with the combined administration of acetylsalicylic acid and dipyridamole. Thromboemboli after diagnostic catheter procedures can be avoided through anticoagulants, and here heparin is the drug of choice. It seems doubtful whether anticoagulation is necessary in every case.

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XI. Cerebrovascular Diseases

Introduction

The treatment of cerebrovascular disorders with drugs which affect the hemostasis system is always a high-risk therapy. For each patient the origin of the cerebral ischemia, the accompanying diseases and the contraindications must be considered, and it must be decided afresh whether anticoagulation or platelet aggregation inhibition is reasonable and feasible. About 80% of brain infarcts are caused by thrombotic and embolic events, and about 10% by intracerebral bleeding.

Of cerebral thromboses and embolisms, 70–80% originate in alterations in the proximal aorta and the extracranial and intracranial carotid circulation. Fig. 1 shows the percentage of extracranial vascular alterations in the carotid-vertebral circulation. 10% of embolisms are cardiac in origin and spring from thrombi which have formed in the region of an infarct, from aneurysms of the heart wall, from fibrillating atria, valvular failure and artificial valves.

Cerebral ischemic attacks may also occur as the result of stenoses of the extracranial and intracranial carotid circulation area caused by arteriosclerosis hemodynamically active, that become during fluctuations in blood pressure, hypotension, circulatory shock and disturbances of heart rhythm, and as a result of the formation of kinks and compression of arteries from outside, inflammatory vascular alterations, thrombocytosis and hyperviscosity syndrome.

Most cerebral ischemia syndromes, especially the transient ischemic attacks which are characterized by fully reversible neurological symptoms lasting from only a few minutes to 24 hours, are assumed to be caused by platelet-fibrin thrombi from vessels altered by arterio-

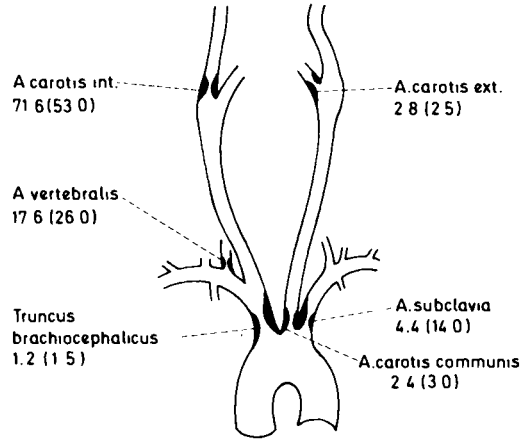

Fig. 1. Percentage frequency of arteriosclerotic stenosis and localization of occlusion in extracranial cerebral arteries in 250 angiograms. In brackets, figures from patient material in vascular surgery (Gänshirt, Reuther, 1979)

sclerosis. The idea that platelet aggregates are mainly concerned has led to extensive reseach on the prophylactic value of platelet aggregation inhibition. Emboli from the area of the carotid circulation are more common than those from the vascular area of the vertebrobasilaris artery. The neurological symptoms differ according to the areas of the brain affected. It follows from what has been said that treatment with anti-coagulants or platelet aggregation inhibitors in cerebrovascular disorders must not be carried out uncritically, but that an exact differential diagnosis explaining the origin is a prerequisite for the treatment to be given. If a cerebrovascular disorder is recognized as the result of a thrombosis or embolism in or from the carotid or vertebral circulatory area, the possible disorders are treated in the following sections (Fig. 2).

Transitory Ischemic Attacks (TIA)

Untreated ischemic attacks recur in the following 2 to 3 ½ years in 20 to 50%, and according to some observations up to 80%. Infarcts occur in

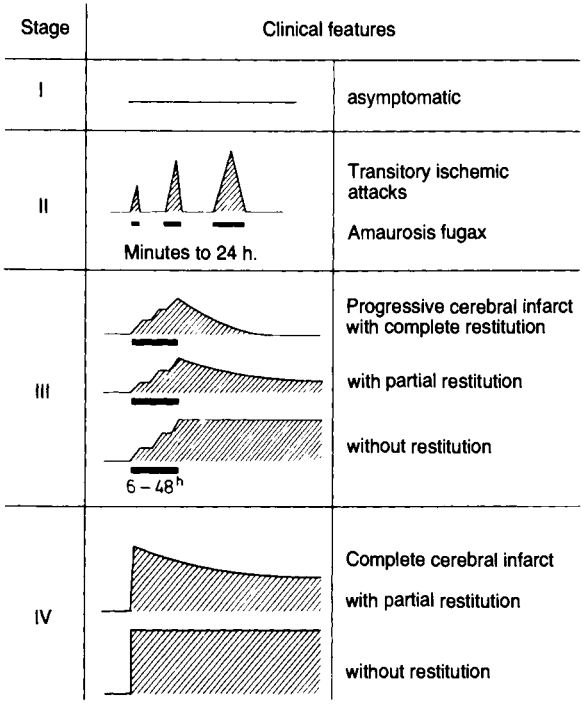

Fig. 2. Course in time of focal ischemic cerebral symptoms (Gänshirt, Reuther, 1979)

10 to 25%, and according to the findings of individual researchers up to more than 50% of cases (Table 1). The aim of coagulation-inhibiting treatment is to prevent transitory ischemic attacks, to reduce their frequency and avoid the transition to a cerebral infarct. A very large number of the studies carried out in the last years with acetylsalicylic acid showed a positive effect in reducing transitory ischemic attacks. Sulfinpyrazone and dipyridamole were not effective on their own, only in combination with acetylsalicylic acid. The clearest effects were observed when series of transitory ischemic attacks occurred. In several studies a reduction in the number of cerebral infarcts and deaths was observed. It is surprising that the prophylaxis was more successful in men than in women (Table 2).

Table 1. Course of untreated transitory ischemic attacks: Frequency of recurrence of TIA and of cerebral infarcts (Ostendorf, 1979)

Study	No. of patients	Period of observation in months	TIA recurrence	Infarct
Fischer (1958)	23	?	4 (17%)	8 (35%)
Siekert (1961)	40	40	10 (40%)	19 (48%)
Baker (1962)	20	20	16 (80%)	5 (25%)
Siekert (1963)	160	60	–	58 (36%)
Marshall (1964)	61	45	–	1 (1.6%)
Pearce (1965)	20	10.6	19 (45%)	2 (10%)
Baker (1966)	30	40.6	14 (47%)	7 (23%)
Baker (1968)	79	41	45 (57%)	17 (22%)
Friedmann (1969)	23	27.4	–	8 (35%)
Fields (1970)	145	42	68 (47%)	18 (12%)
Karp (1973)	28	44	8 (29%)	2 (4.5%)
Dyken (1973)	11	>3	9 (82%)	1 (9%)
Toole (1975)	56	46	15 (27%)	7 (12%)
Fields (1977)	90	6	20 (22%)	10 (11%)
Reuther (1978)	29	24	9 (31%)	4 (14%)

Table 2. Results of several controlled studies with platelet aggregation inhibitors as prophylaxis against cerebral infarct. DP: Dipyridamol; ASA: acetylsalicylic acid; SP: sulfinpyrazone (Dorndorf, Kaps, 1981)

		Substance	Effect
Acheson et al.	1969	DP	–
AITIA study	1977/78	ASA	+[a]
Heidelberg study	1977	ASA	+[b]
Canada study	1978	ASA	+[c]
		SP	–
		SP + ASA	+[c]
Worthington et al.	1978	ASA	+
Memphis study	1979	SP	+
Lund study	1980	ASA + DP	+
AMIS	1980	ASA	+
PARIS	1980	DP + ASA	+
		ASA	+

[a] significant for patients with repeated attacks and arteriosclerotic changes to the carotid vascular walls

[b] significant for carotid, not vertebrobasilar attacks

[c] significant for men, not for women

There are several studies from 1958 to 1965 examining the value of anticoagulation in transitory ischemic attacks. From the point of view of the occurrence of cerebral infarcts and total mortality no differences from the control groups could be found. However, the frequency of recurrence of transitory ischemic attacks fell. We must take into account the fact that the studies were not statistically rigorous. It has not been proved whether in the first 8 weeks from the beginning of the attacks aggregation inhibitors or anticoagulant treatment was superior. There are indications that at least in the first three months an equivalent positive effect in frequent transitory attacks is obtainable through anticoagulants. It has been recommended, after three months on anticoagulants, to change to aggregation inhibitors. Treatment with aggregation inhibitors is to be recommended in any case for the first year after the beginning of the attacks as after that their frequency decreases distinctly and in the first year the danger of a stroke is at its greatest. If the attacks are not reduced by platelet inhibitors, anticoagulants should be given.

Progressive Stroke

In the years 1958 to 1965 there were several studies of anti-coagulant treatment of reversible cerebral ischemia with, however, neurological symptoms increasing over a certain length of time (Table 3). We can deduce, with certain reservations, that the development of the neurological symptoms could be mitigated by anticoagulants. There are no studies with aggregation inhibitors. In these cases, because of the possibility of intracerebral bleeding occurring, special care is necessary, especially as an ischemic insult can be followed by intracerebral bleeding. In general, antithrombotic treatment is to be avoided.

Completed Stroke

In cases of acute complete stroke, research has shown that treatment with coagulation-inhibiting substances is of no use. No reduction of mortality in the acute stage and in the further course of the disease could be obtained, nor of the recurrence of the infarct. The rate of

Table 3. Results of treatment of progressive stroke with anticoagulants in comparison with controls (Ostendorf, 1979)

Study	No. of patients	Death by infarct	Death by bleeding	Progressive infarct	Progression (Total in %)
Fisher (1958)					
Control	14	0	0	9	64%
Treated	14	0	0	3	21%
Fisher (1961)					
Control	49	7	0	14	40%
Treated	51	4	1	7	14%
Carter (1961)					
Control	38	7	0	12	50%
Treated	38	3	0	9	32%
Baker (1962)					
Control	67	10	0	21	46%
Treated	61	5	1	8	23%
Millikan (1965)					
Control	60	25	0	8	52%
Treated	181	12	0	25	20%

complications through intracerebral bleeding is high. Anticoagulant treatment is to be rejected.

During the acute phase of a stroke a very high percentage of venous thrombosis occurs, especially in the veins of the pelvis and legs of the paretic extremity. From the point of view of the prophylaxis of venous thromboembolism, a subcutaneous dose of heparin should be considered in cases of fresh ischemic insult. It was demonstrable that with 3 × 5000 IU of heparin daily, plus 3 × 0.5 mg of dihydergot amine, the frequency of thrombosis could be reduced from 50% to 27.5% without the occurrence of recognizable complications through cerebral bleeding. Mortality was 25% in the placebo group and 15% in the group given the treatment.

If the emboli transported into the brain originate from the heart, obviously consequent anticoagulation therapy to prevent recurrence is indicated, according to the underlying disease. If a cerebral embolism occurs nevertheless, a decision must be made between the following possibilities. Either the coagulation-inhibiting treatment must be discontinued, especially if a secondary cerebral hemorrhage is assumed

or demonstrated or during the acute phase oral anticoagulation treatment must be replaced by subcutaneous heparin. This may be especially urgently necessary in cases of artificial heart valves, so as to prevent further growth of thrombi on the valves. In such cases there may be considerable problems with regard to the therapeutic procedure. The transition to oral anticoagulants should not follow until 6 weeks have passed, and in no case must it be earlier than 2 weeks after the acute event.

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XII. Coagulation Factor Deficiencies with Tendency to Thrombosis

Antithrombin III Deficiency (Congenital and Acquired)

Clinical Findings and Diagnosis

Antithrombin III is formed in the liver. It inhibits first of all factor IIa (thrombin) and factor Xa. In addition factors VIIa, IXa, XIa, XIIa, plasmin and kallikrein are inhibited. The plasma concentration is between 14 mg and 20 mg/100 ml of plasma, or between 80 and 120% of the norm. The biological half-life is 2.8 ± 0.3 days. A drop in antithrombin III to 70–80% of the norm is accompanied by an increased tendency to thrombosis. Antithrombin III deficiency may be congenital or acquired (Table 1).

Congenital antithrombin III deficiency is inherited through an autosomal dominant gene. Its frequency is considered to be one case in about 5000 persons. Antithrombin III, measured in patients by either immunological or functional (chromogenic substrate) methods, lies in the region of 30 to 70% of the norm. Hereditary antithrombin III deficiency is suspected if there is frequent occurrence of thromboses of the deep veins of pelvis and legs within a family, especially if they occur without recognizable external cause, and during the first decades of life. The lack of response to heparin therapy is a further indication of possible antithrombin III deficiency. Up to the 25th year of life about 50%, and up to the 50th year about 80% of those affected have suffered a thromboembolic episode. In about one-third of the patients the thrombosis occurs spontaneously, and in the remaining two-thirds operations, pregnancy, childbirth and estrogen-containing contraceptives are precipitating factors.

Table 1. Causes of an antithrombin III deficiency

Disorder of synthesis	a) Congenital, hereditary b) Acute liver failure c) Hepatic cirrhosis
Consumption	a) Disseminated intravascular coagulation (consumption coagulopathy) b) Circulatory shock c) Sepsis d) Tumors e) Operation f) Venous thrombosis g) Pulmonary embolism
Loss and various causes	a) Nephrotic syndrome b) Plasmapheresis c) Hemodialysis d) Hemofiltration e) Heparin-induced AT III deficiency

Acquired antithrombin III deficiency is relatively common. It appears as the result of a disturbance in synthesis or an increase in turnover in the coagulation system, and through increased loss (Fig. 1). Reduced synthesis occurs in advanced cirrhosis of the liver, acute liver failure (poisoning with amanita phalloides or carbon tetrachloride), hypercatabolic conditions and with ovulation inhibitors containing ethinyl estrogen. Increased consumption occurs in disseminated intravascular coagulation and consumption coagulopathies of whatever origin (shock, cirrhosis of the liver – combined with disturbance of synthesis –, sepsis), in patients with tumors, after major operations (particularly hip replacement, extracorporeal circulation), in the course of recurring thromboembolisms and long-term heparin therapy. After operations and acute cardiac infarct the lowest value is reached after 1 to 3 days, and after that the antithrombin III level rises again. An increased loss is observed in a nephrotic syndrome with daily loss of protein of 4–5 g, after plasmapheresis and hemorrhagic shock with massive transfusions. In these conditions, determination of the antithrombin III level is indicated.

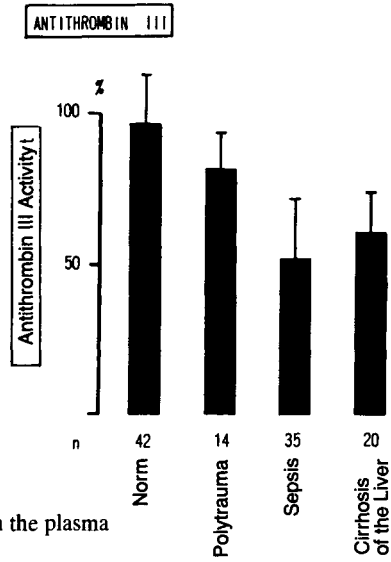

Fig. 1. Antithrombin III activity in the plasma in various diseases

Treatment

In hereditary antithrombin III deficiency, longterm treatment with coumarin derivatives is the method of choice. If thromboembolic complications occur, and in the case of acquired antithrombin III deficiency, heparin therapy is to be recommended; if there is no response antithrombin III preparations should be substituted. In substitution with antithrombin III concentrates, the level should be above 80% of the norm. With one unit of antithrombin III per kg of body weight, the antithrombin III concentration can be raised by 1 to 2%. The initial dose is about 1500–2500 units of antithrombin III. About the same amount should be substituted daily in fractional doses, under control of the antithrombin III level. The dose should be adjusted to the turnover rate. In the case of consumption coagulopathy and disseminated intravascular coagulation with total breakdown of the potential for hemostasis, the substitution of fibrinogen, Cohn's fraction and prothrombin complex preparations may be necessary. These

may promote the activation of coagulation; with antithrombin III probably an effective suppression of pro coagulatory stimulation is possible, and the dose of heparin to be given can be reduced.

Protein C and Protein S Deficiencies

Protein C was first described by Mammen and Seegers in 1960 as autoprothrombin II-A, and since 1976 it has been again researched and characterized in more detail. Protein C is a protein formed in the liver, and, like the prothrombin complex, its synthesis depends on vitamin K. It has a molecular weight of 62,000 Daltons. It is a serine protease activated by factor Xa and thrombin. The activation can be speeded up 20,000 times by thrombomodulin. Activated protein C (Ca) specifically inactivates activated factors V and VIII by limited proteolysis. In this way it has an inhibiting effect on the process of coagulation and can be considered a regulating protein in hemostasis. Its activity is regulated in turn by protein S. The normal plasma level of protein C is between 0.65 and 1.45 U/ml. With immunological methods the quotient of protein C to prothrombin and factor X is 1. Under anticoagulation treatment with coumarin derivatives the protein C plasma content falls, together with the factors of the prothrombin complex, and the quotient mentioned remains more or less unaltered at 1. In recent years a few families with isolated protein C deficiency, suffering from recurrent thromboembolisms, have been described. In these patients the protein C concentration was below 0.65 U/ml. If these patients are given coumarin derivatives as prophylaxis against thromboembolism, the quotient of protein C and prothrombin and factor X is considerably below 1. Protein C also stimulates fibrinolysis by inhibiting the t-PA-inactivator, so that the tendency to thrombosis in protein C deficiency results from the combination of reduced coagulation inhibition and restricted fibrinolysis. A reduction in Protein C also occurs postoperatively, in advanced cirrhosis of the liver and in disseminated intravascular coagulation.

A deficiency of an inhibitor for the action of protein C has also been described, with increased destruction of coagulation factors V and VIII. This lack of an inhibitor is said to be responsible for some cases of hemophilia with combined deficiency of factors V and VIII with only 20 to 30% of normal activity. The pathological changes from coagula-

tion analysis linked with these factor deficiencies are described elsewhere. There is an increased propensity to bleed.
A deficiency of protein S is accompanied by a thrombophilia. In the cases observed to date the protein S level in the plasma lay between 15% and 37% of the norm.

Fibrinolysis Defect

There are some case reports on a reduced release of tissue plasminogen activator (tPA) into the plasma and on a both structurally and functionally abnormal plasminogen. There is an increased tendency to thrombosis.

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C. Substances Active in Clotting

XIII. Side Effects, Hemorrhagic Complications, Contraindications, and Tolerance Changes for Anticoagulants, Aggregation Inhibitors, and Fibrinolytics

Side Effects and Intolerance Reactions

In this context side effects are defined as those signs and symptoms that have no direct relationship to the intended therapeutic effects of the drugs.

Heparin

In addition to headache, back pains, joint pains, and fever, one finds urticaria, pruritus, nausea, vomiting, dyspnea, bronchospasm, tachycardia, and blood pressure reduction. The reactions are however mostly slight. In rare cases, one gets circulatory shock. The data on the frequency according to the literature for the years between 1942 and 1964 indicate rates of 1 to 5%, with a maximum of 10%. The hypersensitivity reactions occur mostly within ½ to 2 h after intravenous injection and disappear spontaneously after a few hours. They also occur frequently after the first injection of a heparin preparation or during a short treatment. The causes lie less often in the heparin itself than in impurities, particularly proteins, which in previous times produced the effects because of imperfect preparation techniques and preservatives. In spite of similarities in the clinical picture to anaphylactic reactions, immunological and allergic mechanisms are less likely to be responsible. There is a rise in the transaminases, whose origin is unclear, which reaches its peak between the fifth and eighth day and

then spontaneously declines. Hair loss to various extents occurs in 5 to 40% of patients at four to six weeks after the start of the treat ment.

This alopecia is reversible in all cases. Further, at 15 to 45 min after the intravenous injection of heparin, one can get acute states of pain, which are assumed to be vascular crises. The pains are localized either in upper or lower extremities and can affect both hands, the head, and also the radiation region of infarct pain. There is some preference for the leg containing the thrombosis for which the heparin has been given. The extremity becomes cyanotic or ischemic. The symptoms vanish after some hours without giving rise to persistent circulation disorders or additional thromboembolic complications. Protamine can reduce the duration of the vascular spasm. There is at present no explanation of the cause. Reports of this kind do not occur in the more recent literature.

Thrombocytopenia occurs in patients receiving heparin, which occurs either after the first injections on the first or second day of the treatment or up to three to 20 days after the start of therapy or of subcutaneous prophylaxis. In the first case, the fall in the platelet count is usually slight to moderate. It is rare to observe thrombopenia less than 100,000 per mm^3. A hemorrhagic pattern is not observed. The platelets mostly recover to the initial value after some time in spite of heparin being continued. The platelet fall is for the most part clinically unimportant. It occurs in from 2 to 20% of patients. An allergic cause has not been detected. It is assumed that heparin has a platelet-aggregating capacity, which leads to platelet destruction or to sequestration in the spleen or in the vascular periphery. Frequently, it is not possible to make a distinction from thrombocytopenia accompanying an underlying disease. The second form of thrombocytopenia described in the literature occurs after more prolonged intravenous and subcutaneous heparin. According to the available prospective studies, the frequencies of thrombocytopenia with values less than 100,000 to 150,000 per mm^3 is from 1 to 6% (heparin from intestinal mucosa), but according to some studies it is 20% or even 30% (heparin from bovine lungs). When the heparin is withdrawn, the platelets in each case recover to the normal value after two to three days. Platelet transfusion is without value if the intravenous or subcutaneous heparin is continued as regards the platelet count and the hemorrhagic diathesis. From the clinical viewpoint, it is recommended that a platelet

count should be done after about five to seven days of intravenous or subcutaneous heparin. It is notable that thrombocytopenia is more common when one uses heparin from bovine lung in comparison with preparations derived from porcine gut mucosa. The reasons for this following prolonged heparin administation giving rise to thrombopenia have not been finally established, although it has repeatedly been suggested that immunological mechanisms are responsible. In the Federal Republic of Germany, the only heparin used is that derived from gut mucosa.

There are reports of skin necroses occurring several days after intravenous heparin at various points on the body, but particularly at the site of injection after subcutaneous administration. In the latter case, some hours after the injection, there is painful swelling and reddening, and then at about 24 h, central necrosis in the skin and underlying fatty tissues. The areas may be several centimeters in diameter. Histology mostly reveals only necroses with associated hemorrhage, but sometimes there are inflammatory vascular changes, which are of reactive type, or else one sees pictures with venous and capillary thrombi without inflammatory systems, which resemble the Shwartzmann reaction.

In addition to hemorrhages, more prolonged intravenous and subcutaneous heparin can give rise to thromboembolic complications during the thrombocytopenia phase, in part with manifest hemorrhage. This involves leg vein thromboses, lung embolism, myocardial infarction, and frequently arterial thrombotic obstruction, which may make amputation necessary. In these reports, there appears to be no relationship between the thromboembolism and the underlying disease, although there is mention of consequences of clotting activation in the course of platelet decrease. Following change to coumarin derivatives, the thromboembolic process can be halted. In some cases, laboratory analyses indicate activated clotting and fibrinolysis during the phase of thrombocytopenia, with decrease in fibrinogen and increase in fibrin cleavage products.

When heparin is given for several months to half a year or more, one can get diffuse osteoporosis, which can lead to spontaneous fracture of vertebral bodies. If heparin is combined with dihydergotamine in the subcutaneous prophylaxis of thromboembolism, one has to envisage the possibility of vascular spasm in the extremities and the provocation of angina pectoris attacks under certain circumstances.

Coumarin Derivatives

Treatment with indirect anticoagulants can give rise to hair loss, urticaria, dermatitis, capillary damage, and gastrointestinal symptoms, with nausea, loss of appetite, vomiting, and diarrhea. Sometimes, the transaminases are elevated. In rare cases, one gets skin necroses between the third and fourth days, but never after the tenth day. These occur mostly in females. The preferred sites are the thigh, skin of the stomach, buttocks, and mammae. Following initial swelling with central reddening, some hours later one gets hemorrhage, and finally sharply delimited necrotic areas of the size of small coins after a few days. The vessels are thrombosed in these areas. There have been discussions of pathogenetic relationships between coumarin necroses and protein C deficiency. Therapeutic trials have been performed with cortisone, heparin, and fibrinolysis. One may mention the so-called warfarin embryopathy in mothers who have taken coumarin derivatives during the first weeks of pregnancy. The symptoms include microcephaly, optic-nerve atrophy, and nasal hypoplasia.

Aggregation Inhibitors

Acetylsalicylic acid can produce urticaria and bronchial asthma. In about 25% of cases, one observes gastrointestinal pains (stomach pains, nausea, and vomiting), especially when the drug is taken during fasting. The gastrointestinal symptoms are less common with sulfinpyrazone.

Dextrans

In rare cases, anaphylactoid and anaphylactic reactions are observed. The first are not of immunological type and are due to direct release of vasoactive mediators produced by the dextran. Anaphylactic reactions are produced by preformed antibodies. The reactions occur also in people who have had no previous contact with dextrans. The clinical symptoms range from urticaria, erythema, bronchospasm, and blood pressure drop to circulatory shock, cardiac arrest, and death. Dextran

1000 (Promit) can act as hapten; it is given in a dose of 20 ml before the start of the dextran infusion and neutralizes the antibodies, which enables one largely to avoid anaphylactic reactions.

Fibrinolytics

Urokinase does not give rise to intolerance reactions, except sometimes a temperature rise, which does however occur more often with streptokinase. Early reactions with streptokinase include temperature rise, joint and back pains, exanthema, flushing, tachycardia, and blood pressure fall. These symptoms were observed in 25.4% of patients, but they did not lead to the treatment being terminated. Temperature rises above 38.5° occur in 17.4%; these tend to increase with the duration of the treatment (Tilsner 1975). Sometimes, one gets exanthema and bronchospasm, and also rises in the transaminases and in the alkaline phosphatase.

Hemorrhagic Complications

If the hemostasis system is initially intact, intravenous heparin treatment can produce up to 7.6% incidence of mainly moderate hemorrhage. If the hemostasis is initially perturbed, this occurs in up to 50% of patients. Usually, the reports give no indication of the duration of the individual treatment. With low heparin doses of about 15,000 I.U. subcutaneously or intravenously, one seldom gets spontaneous hemorrhage. The incidence increases with the dose and becomes relatively common at doses of 40,000 I.U. and more. The bleeding frequency also increases with intermittent intravenous heparin doses and in long-term heparin treatment.
With coumarin treatment, the incidence of hemorrhage is 4.3% per treatment year. With 5½ to 16 treatment years, one gets one more pronounced and threatening hemorrhage. One lethal hemorrhage occurs within from 71 to 461 treatment years. The numbers quoted by the well-organized Dutch thrombosis service are the most favorable. The complication rates in other countries appear to be higher. With coumarin treatment, the hemorrhages occur in from 54 to 64% of cases in areas of localized disease such as ulcers, carcinomas, gut diverticu-

Table 1. Localization of spontaneous hemorrhage with coumarin and heparin treatment

1. Urinary pathways
2. Gastrointestinal tract
3. Nasopharyngeal space
4. Eyes (retina and subconjunctival area)
5. Menorrhagia, metrorrhagia
6. Central nervous system (epidural, subdural, intracerebral, spinal)
7. Skin
8. Musculature, joints
9. Respiratory tract
10. Gut wall
11. Retroperitoneal space
12. Hemorrhoids
13. Hematothorax
14. Adrenals (mainly with heparin)
15. Ovaries (mainly with coumarin)
16. Hemobilia

loses, and stones in the urinary pathways. In 23 to 33% of the cases, there is auxiliary medication, which increases the bleeding risk. In 13% of cases, no special reason could be established.

Table 1 lists the localization of spontaneous bleeding with coumarins and heparin. Some of the localizations are very rare (ovaries and adrenals). With coumarin, hematuria (40%) is the commonest, followed by bleeding into the gastrointestinal tract and in the nasopharyngeal space (18% each), and in the occular region (13%). The proportion in the central nervous system is 3%.

Hemorrhage is very rare with dextran infusion. It occurs only when there is existing hemorrhagic diathesis or simultaneous administration of other substances affecting the hemostasis system.

Bleeding into the gastrointestinal tract is prominent with platelet aggregation inhibitors. The bleeding frequency increases for patients undergoing coagulation-inhibiting treatment, who have an elevated hemorrhage risk (liver cirrhosis and terminal renal disease) or a preexisting hemorrhagic diathesis.

With streptokinase (initial dose 250,000 I.U., maintenance dose 100,000 I.U. per hour) used in 708 cases to produce fibrinolysis on

account of chronic arterial occlusive disease, there were 209 instances (29.5%) of bleeding complications. Of these 156 (22%) were minor and did not lead to the treatment being terminated; 53 (7.5%) were more severe and led to the fibrinolysis being terminated; five (0.7%) were lethal. The sites were as follows: eight (1.1%) intestinal, 57 (8.1%) urological, 10 (1.4%) intracranial of which five (0.7%) were lethal, and 134 (18.9%) were hemorrhages at other sites (site of puncture, etc.) (Tilsner 1975). The frequency increased with the duration of the fibrinolysis. In the treatment of venous thromboses, the frequencies were lower, especially of severe bleeding, because the patient group on average was younger and thus showed fewer risk factors. In all, in about 14% of cases, the fibrinolysis had to be terminated (hermorrhage, fever, elevated antistreptokinase titer). The frequencies of hemorrhage and other side effects are lower in fibrinolysis with urokinase.

Contraindications and Restricted Indications

Situations are relatively rare where the treatment with anticoagulants, aggregation inhibitors, dextran, hydroxyethyl starch compounds, and fibrinolytics is absolutely not indicated. The decision in favor of or against intervening in the hemostatic system and for a given drug is dependent on the type and severity of the accompanying underlying disease and the scale of the thromboembolic complications. With suitable supervision and obedience to all the precautions, one can carry out antithrombotic and fibrinolytic treatments even in the presence of diseases usually representing contraindications.

Although the contraindications given in Table 2 in principle apply for all clotting inhibitors and fibrinolytics, there are differences in bleeding hazard. One can select the drug most suitable for the situation or can alter the drug and can initiate and end the treatment at suitable times in order to largely avoid complications.

Consumptive coagulopathy is usually an indication for anticoagulation with heparin. If there are healed gastrointestinal ulcers without tendency to recurrence, there is no contraindication to anticoagulant treatment. If there is manifest hemorrhage, one can carry out a treatment with heparin and dextran of short duration if local hemostyptic measures are possible. In advanced liver disease or liver cirrhosis, one

Table 2. Contraindications and limited indications for treatment with anticoagulant medicaments

1. Hemorrhagic diathesis (coagulopathy, thrombocytopenia, thrombocytopathy)
2. Hemorrhage anywhere in the body
3. Gastrointestinal ulcer
4. Cirrhosis and advanced diseases of the liver
5. Hypertension (systolic/diastolic pressure > 200/115 mmHg)
6. Advanced retinopathy (hypertension, hemorrhage of the fundus)
7. Renal insufficiency
8. Nephrolithiasis
9. Leukemia
10. Bacterial endocarditis
11. Trauma, polytrauma, recent operation
12. Recent apoplexy
13. Operation on the central nervous system
14. Puncture of arteries or parenchymal organs
15. Aortic aneurysm
16. Pregnancy
17. Acute pancreatitis
18. Malabsorption syndrome
19. Cavernous pulmonary tuberculosis
20. Combination of anticoagulants
21. Chronic alcoholism
22. Lack of cooperation

has to consider the involvement of the hemostasis system or the prothrombin time, respectively. Well-treated hypertension without secondary complications such as retinopathy allows anticoagulant treatment. In dialysis patients, terminal renal insufficiency may make it necessary to keep the shunt open by anticoagulant treatment with coumarins. It must be remembered that coumarins are dialyzable. In trauma, it is usually indicated to give perioperative thrombosis prophylaxis with low-dose heparin and dextran. In ischemic brain infarct, low-dose heparin has been employed successfully in thrombosis prophylaxis. In operations on the central nervous system, anticoagulant treatment can be started after at least 14 days. Fibrinolysis following operative intervention is usually possible after eight to 14 days, while after injury or operation on the central nervous system, only after six to eight weeks. Fibrinolysis should be initiated not before

seven days following puncture of superficial arteries. The delay should be at least 14 days following aortal puncture. One is not justified in using anticoagulant treatment with coumarin derivatives during pregnancy in the first three months, because of the warfarin embryopathy, or in the last three months, on account of the hemorrhage hazard for mother and child. In any case, heparin treatment is to be preferred during thromboembolic complications, and should be broken off only for a short time during parturition. Platelet aggregation inhibitors should be withdrawn 10 days before the expected date of birth. There is a relatively elevated hemorrhage risk in fibrinolysis treatment directly postpartum. If there is severe acute pancreatitis, there is a very high risk of hemorrhage. The malabsorption syndrome is a contraindication for oral anticoagulants. Caution is required in each case of combining various drugs with anticoagulants.

Treatment of Hemorrhagic Complications

(see also Chapter XIV)

The treatment is dependent on:

1. hemorrhage location
2. hemorrhage severity
3. intensity of the anticoagulant treatment
4. the indication for anticoagulant treatment, i.e., the hazard to the patient from thromboembolic disease that has already occurred or may occur
5. possible existing coagulation disorder.

If there is slight bleeding, one should use local measures as far as possible or halt the treatment for a certain time. With coumarin derivatives, it is appropriate to give a single dose of from 3 to 10 mg of Konakion (Table 4, Chapter XIV).

If the hemorrhage is more pronounced, repeated small doses of protamine chloride intravenously are indicated in subcutaneous heparin administration. With intravenous heparin, one gives protamine chloride equivalent to 2/3 of the dose last given or that given in the previous 12 h, e.g., 10 ml of protamine 1,000 for 15,000 units of heparin. As protamine is metabolized more rapidly than heparin, a

follow-up injection may be necessary. One should avoid overdosage on account of the anticoagulant effect of protamine chloride.
If there is extensive hemorrhage produced by indirect anticoagulants, one is justified in giving single or multiple doses of 10–20 mg of vitamin K orally or intravenously (caution: circulatory reaction). A rise in the Quick value by 40 to 50% is appropriate. Excessive vitamin K doses are undesirable, since the vitamin K regeneration cycle will be overstimulated, and resetting the anticoagulant treatment is made complicated over a more prolonged period. It may be necessary to give vitamin K repeatedly, since overdosage of coumarins can lead to the uptake of coumarin from the gut persisting for days. The enterohepatic circulation can be halted with cholestyramine (8–12 g/d). Prompt hemostasis is provided by a prothrombin complex preparation (2,000–8,000 units per day). Subsequent substitution is necessary on account of the short biological half-lives of the clotting factors, until there is a rise in the Quick value. The effects of aggregation inhibitors can be eliminated only by the use of fresh blood, plasma rich in platelets, or platelet concentrates. The fibrinolysis effect of streptokinase or urokinase can be inhibited by giving from 500,000 to 1000,000 K.I. units of Trasylol, with a follow-up hourly infusion of from 50,000 to 100,000 K.I. units until the fibrinolytic action declines. Alternatively, one can give 6 to 12 g of ε-amino caproic acid or 1 to 4 g of AMCHA per day distributed as several doses (Table 6, Chapter XIV).

Changes in Tolerance for Anticoagulants due to Interactions with or Interference from Other Drugs

Only coumarin derivatives show interactions with other drugs in the sense of accentuation or diminution of the effect. In all other cases, there is accentuation of the anticoagulant effect and the hemorrhagic picture via independent mechanisms with different points of attack. In one-third of patients treated with oral anticoagulants, they receive one or more drugs affecting the action of coumarin. Barbiturates account for 61%. The relevance of interaction should therefore be critically evaluated. Only a restricted number of drugs will interfere with oral anticoagulants on a scale that leads one to fear acute unexpected hemorrhagic complications.

Table 3. Substances with pharmacodynamic interaction with coumarin derivatives (Matthias 1981)

Vitamin K availability:
neomycin, colchicine, cholestyramine, antibiotics, malabsorption syndrome
Increased synthesis of clotting factors:
steroids, estrogens
Inhibition of clotting factor synthesis:
anabolic drugs, glucagon
Increase in clotting factor metabolism:
thyroxine, anabolic drugs

Table 3 lists substances showing pharmacodynamic interaction with coumarin. Neomycin and colchicine affect the uptake of vitamin K by damage to the gut mucosa. Long-time high-dose antibiotic treatment eliminates the physiological gut flora, and the vitamin K synthesized by bacteria in the gut is no longer available. It is questionable how far this is of clinical significance. Certain third-generation cephalosporins containing thiotetrazole side-chains produce a reduction in the Quick value (e.g., Latamoxef). In addition to the above modification of the gut flora, there is direct inhibition of the synthesis step for the prothrombin complex factors dependent on vitamin K. Vitamin K substitution eliminates the clotting defect (10 mg of vitamin K per week in long-term antibiotic treatment). Poor digestion and malabsorption reduce the vitamin K uptake. Cholestyramine restricts the uptake of the fat-soluble vitamin K by binding cholesterol and bile acids. There are also effects on the synthesis of clotting factors from estrogens and anabolic drugs, as well as glucagon and thyroxin, but they do not have any great significance for the management of anticoagulant treatment. After the elimination of cardiac insufficiency, the uptake capacity of the gut increases, as does the synthesis of the clotting factors in the liver. An elevated anticoagulant requirement is then usually necessary.

Table 4 indicates pharmacokinetic interactions with coumarins. Cholestyramine absorbs coumarins in the gut, hinders their uptake, and can reduce the plasma level for phenprocoumon (Marcumar) by up to 50%. The inhibition of the entrohepatic circulation for coumarins may increase the elimination by a factor 1.5 to two. Cholestyramine has uses in the treatment of coumarin intoxication. The uptake

Table 4. Substances with pharmacokinetic interaction with coumarin derivatives (Matthias 1981)

Reduction in bioavailability:
cholestyramine, antacids, activated charcoal
Displacement from protein:
phenylbutazone, oxyphenbutazone, sulfonamides, oral antidiabetic drugs, indomethacin, clofibrate, ethacrynic acid, chloral hydrate
Increase in metabolism:
barbiturates, glutethimide, rifampicin, carbamacepin
Metabolic inhibition:
allopurinol, cimetidine, chloramphenicol, disulfiram, metronidazole, oxyphenbutazone, phenylbutazone, salicylate, sulfonamides, clofibrate

of vitamin K is also affected, so reduced coumarin effects are partly compensated. Antacids and activated charcoals appear to have no clinically relevant effects. With phenylbutazone and oxyphenbutazone, the displacement of the coumarin from protein binding has only a subordinate effect (see later). Phenylbutazone stimulates the metabolism of the weakly active R (+) enantiomer of warfarin (Coumadin) and inhibits the clearance of the S (−) enantiomer, which is more active by a factor three to five. The plasma level of the last rises, and the effect is increased. Metronidazol (Clont, Flagyl) produces also delayed elimination of S (−) warfarin, but it appears to leave R (+) warfarin unaffected. There is consequently an increase in the effect. Phenprocoumon (Marcumar) can in both cases show an analogous stereoselective mechanism. Clofibrate (Regelan) can make it necessary to halve the therapeutic dose of coumarin. Clofibrate inhibits coumarin metabolism, displaces the coumarin from protein binding, and elevates the receptor sensitivity to coumarin. It has been suggested that there is an increase in receptor sensitivity and an increase in the metabolism of the prothrombin complex produced by bezafibrate (Cedur). Sulfonamides inhibit coumarin metabolism and accentuates its effects by displacing it from protein binding. It may be necessary to adapt the dose at the start and end of intermediate treatment with Bactrim, Eusaprim, or Omsat. These drugs contain sulfonamide derivatives, along with sulfisoxazole and sulfamethoxazole. Coumarins inhibit the metabolism of certain oral antidiabetic

drugs and release them from protein binding. Hypoglycemia occurs in the simultaneous administration of coumarins. It has not been demonstrated whether the converse effect occurs: accentuation of the action of coumarin. Cimetidine (Tagamet) inhibits the metabolism of warfarin and usually requires the dose to be reduced. Ranitidine (Sostril, Zantic) has not yet been the subject of sufficient experience. Sulfinpyrazone (Anturane) displaces coumarin from protein binding and increases the metabolism. On account of the modest inhibition produced by allopurinol on metabolism, there is a danger of hemorrhagic complications only after a fairly prolonged period, where an appropriate dosage adjustment may be made. Chloramphenicol appears to have a more pronounced inhibiting effect on anticoagulant metabolism, and this results in phenprocoumon overdosage after four to five days, with the Quick value falling below the therapeutic range. If the drugs were given before start of therapy with oral anticoagulants the interaction would not have been observed or only observed after the end of therapy by an increase of anticoagulant demand. Increased coumarin metabolism can be produced by enzyme induction for the drug-metabolizing mixed-function oxygenases in the liver, where barbiturates have been examined as the most significant. This means that the effects of the anticoagulants are reduced, which can require a dose increase of up to 50%. When the barbiturate is withdrawn, weeks may pass before the metabolic rate falls to the previous level.

Drug interactions involving displacement from protein binding have a clinically relevant effect only when the protein binding of the drug is over 90%. Protein binding of coumarin derivatives is between 90 and 99%. With 99% binding of phenprocoumon (Marcumar), the release of 1% would double the pharmacological active amount, and correspondingly the pharmacologically active concentration of the free substance would be 2% of the total amount. The peak accentuation of coumarin derivative effects is attained after three to five days. The elevated free concentration implies increases in metabolism and elimination, so a new equilibrium state sets in after about two weeks. There is a bleeding hazard only at the start of additional medication and one of inappropriate anticoagulant response only at the end. Dose adaptation is needed only for a short time in these cases. In contrast to butazolidine derivatives, there is no sufficient evidence for relevant interaction with coumarins in the case of the other antirheumatic and antiphlogistic drugs such as diclofenac (Voltaren), tolmetin (Tolec-

tin), naproxen (Proxen), ibuprofen (Profen), and indomethacin (Amuno). Sulfinpyrazone (Anturane) has an inhibiting effect on metabolism. These compounds, particularly butazolidine derivatives, tend to damage the mucosa and produce ulcers in the gastrointestinal tract as well as inhibition of platelet function, and they also show the above effects in combination with anticoagulants, so they are of appreciable significance as regards bleeding hazard. Less clinical significance attaches to the inhibition of platelet function by chlorpromazine, beta-receptor blockers, and dipyridamol. Clinical significance can attach to the effect on platelet function from dextran and especially from high-dosage penicillins, carbenicillins, and cephalosporins. If there is long-term simultaneous treatment with antiphlogistic drugs, antirheumatics, so-called aggregation inhibitors, and oral anticoagulants or heparin, one has to consider the clinically relevant hemorrhagic diathesis. Sometimes, one finds anticoagulant resistance without interaction with other drugs. This may be due to inhibition of vitamin K epoxide reductase, impaired coumarin utilization at high plasma levels, or delayed uptake and accelerated excretion with low plasma levels.

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XIV. Mode of Action and Characteristics of Some Coagulation-Active Drugs and Their Dosage

Inhibitors of Platelet Function

Acetylsalicylic Acid

Proprietary names: Aspirin, Colfarit, Godamed, Monobeltin. The acetyl-group of acetylsalicylic acid is transferred to a series of plasma proteins (albumin, globulin, hemoglobulin, platelet proteins). The functional limitation of the thrombocytes depends on inhibition of their cyclooxygenase by acetylation of this enzyme. The transformation of arachidonic acid into the prostaglandin peroxides PGG_2 and PGH_2 is inhibited, so no thromboxane A_2 is formed. The formation of further prostaglandin derivatives, such as $PGF_{2\alpha}$, PGD_2 and PGE_2 also does not occur. The two latter substances have an antiaggregatory effect. Moreover, through inhibition of the cyclooxygenase of the endothelium of the vessel wall, no prostacyclin is synthesized. For inhibition of the vessel wall cyclooxygenase higher doses are necessary than for inhibition of the platelet cyclooxygenase. After a single dose of acetylsalicylic acid the activity of the cyclooxygenase in the vessel wall is again demonstrable after a shorter time than in the platelets. Because in animal research after high doses of acetylsalicyclic acid a transitory thrombotic tendency occurred, and some workers showed a shortening of the bleeding time in man, the opinion arose that a better antithrombotic protection was guaranteed by daily low doses or intermittent administration. The research results mentioned could not be verified by other workers, so that next the therapeutic dose remained to be administered at 1–1.5 g/day. Studies with daily doses of 50–100 mg are in progress.

Platelet adhesion is not inhibited by the usual doses. The shape change of the thrombocytes is absent. Aggregation is inhibited in different ways and to a different intensity depending on the precipitating stimulus. The second wave of ADP-induced aggregation is absent. Whereas the aggregation is inhibited by small amounts of thrombin, it is scarcely affected by high thrombin concentrations. Likewise, the inhibition of platelet aggregation by collagen is dose dependent. The release reaction is variably influenced. The bleeding time is prolonged. A shortened thrombocyte survival time is not normalized. Moreover acetylsalicylic acid is said to inhibit phospholipase A_2 and thereby the liberation of arachidonic acid from the platelet membrane.

Further Nonsteroidal Anti-inflammatory Drugs

Indomethacin (Amuno), phenylbutazone (Butazolidin), flurbiprophen (Froben) and related compounds also display their effects by the inhibition of cyclooxygenase. Aggregation due to thrombin, collagen, and arachidonic acid is inhibited, likewise the second wave of aggregation due to ADP or epinephrine. Indomethacin and sulphinpyrazone (Anturan) inhibit platelet adhesion to collagen and subendothelial structures. Moreover, indomethacin inhibits phospholipase A_2 of the thrombocytes. With simultaneous administration of coumarin derivatives the displacement from protein binding by anti-inflammatory drugs must be taken into account; the anticoagulant action is strenghtened.

Dipyridamole

Proprietary names: Persantin, Asasantin (combination preparation with acetylsalicylic acid). Dipyridamole becomes bound to the platelet membrane. It inhibits adenosine uptake into the thrombocytes. The phosphodiesterase becomes inhibited and thereby the breakdown of cyclic AMP. Platelet adhesion and collagen-induced aggregation are reduced in a dose-dependent manner. A shortened thrombocyte survival time becomes normalized. The release-reaction becomes inhibited. Acetylsalicylic acid strengthens the effect of dipyridamole. The therapeutic dose of dipyridamole amounts to 3×75 mg/day.

Ticlopedine

Proprietary name: Ticlid. The mechanism of action is not clearly explained. In contrast to the usual thrombocyte aggregation, the substance does not act *in vitro*. The action *in vivo* is still detectable about 4 days after the last dose. The action must proceed by an intrathrombocytic increase of cyclic AMP. The first wave of aggregation through ADP and epinephrine becomes inhibited. The collagen induced aggregation likewise becomes inhibited. The bleeding time becomes prolonged. The beginning of the full action after oral administration is first attained after 1–3 days. The therapeutic dose is 1–2×250 mg/day.

Sulfinpyrazone

Proprietary name: Anturan. Sulfinpyrazone has structural similarities to phenylbutazone. The uricosuric action has been used for years. The substance inhibits the thrombocytic prostaglandin synthesis competitively. The prostacyclin synthesis of the vessel wall is less affected. Sulfinpyrazone normalizes a shortened thrombocyte survival time and prolongs the bleeding time. The aggregation of thrombocytes *in vitro* becomes inhibited. The therapeutic dose amounts to 3–4×200 mg/day.

Anticoagulants, Fibrinolytics, and Their Inhibitors

Heparin (Unfractionated, UF Heparin)

Proprietary name: Liquemin, Thrombophob, Heparin[1]. Heparin is an acid mucopolysaccharide of variable chain length with a molecular weight range of 2,500–33,000 Daltons. The highest anticoagulatory action lies in the middle region of 13,000–15,000 Dalton. 1 mg of the International Heparin Standard corresponds by definition to 130 International Units (I.U. = USP-U) regardless of the method of determination. The activities of the heparins of different manufacturers are related to the International Standard Heparin. They lie

1 With name of the firm

between 130–170 I.U./mg heparin. The commercial preparations are obtained from the intestinal mucosa of pigs. Heparin from cattle lungs is scarcely still used on account of the more frequent side effects. Heparin is available as sodium or calcium salt. Significant differences with regard to action and side effects do not exist. After administration it is partly taken up into the vascular endothelium and lung and slowly liberated. This can lead to a gradually increasing heparin level and a prolongation of the thrombin time in long duration subcutaneous heparin therapy. Heparin administration by inhalation, in principle possible has so far proved a failure. Heparin binds to serine proteases, accelerates the association of antithrombin III to these proteases and stengthens their action. Factors Xa, and IIa (thrombin) are especially inhibited, but also Factors XIIa, XIa, and IXa. One microgram heparin, together with one microgram antithrombin III inhibits, 32 U Factor Xa and thereby indirectly 1,600 U Factor IIa.

In this way the relatively low amount required for thrombosis prophylaxis is explained. If thrombin was formed and a thrombosis is present, considerably higher quantities of heparin are necessary for thrombin inhibition and inhibition of the progression of thrombosis.

Administration takes place by the subcutaneous or continuous intravenous route. The intermittent intravenous injection at intervals of 4–6 h or 8 h is largely abandoned, due to the increased bleeding tendency associated with the transitory peak concentrations which occasionally occur. For thrombosis prophylaxis the daily subcutaneous heparin administered amounts to 2–3×5,000–7,500 I.U. In internal medicine patients a dosage of 3×7,500 I.U. is recommended because of the usually low bleeding tendency. Patients over 80 kg in body weight receive the higher dosage in each case.

In surgical patients 10 h and/or 2 h, before the beginning of the operation 5,000 I.U. are injected, and then from 6–8 h after the operation at 8–12 h intervals in each case a further 5,000 I.U. over a period of 8–10 days or until complete mobilization of the patient or adequate coumarin action. After implantation of hip joint prostheses the dose is increased to 3×7,500 I.U. on the 3rd postoperative day. The same amount is given in the 3rd trimester for thrombosis prophylaxis in pregnancy. In gynecological operations, in general surgery, urology and neurology the standard dosage amounts to 3×5,000 I.U./day. By combination with 0.5 mg dihydroergotamine, by means of which an accelerated venous return is obtained, the daily amount of

heparin can be reduced with similar prophylactic effect, probably to 2×5,000 I.U. or 3×2,500 I.U. With intravenous administration the daily amount required for thrombosis prophylaxis is about 20,000 I.U., corresponding to 250–300 I.U./kg in 24 h. An effective post-operative thrombosis prophylaxis with a so-called "ultra low-dose" heparin administration of 1 I.U./kg body weight and hour, corresponding to 1,500–2,000 I.U./day, seems to be possible. For the therapy of a thrombosis 20,000 I.U.–40,000 I.U. are necessary, i.e. heparin amounts up to about 600 I.U./kg and 24 h. With severe lung embolism a maximum of 60–80,000 I.U./day is infused. An initial bolus injection of 5,000–10,000 I.U. heparin is the rule. With consumption coagulopathy the heparin requirement amounts to 10–15,000 I.U./day corresponding to 150–200 I.U./kg and 24 h. With intermittent intravenous administration 2,500–10,000 I.U./every 4–6 or 8 h are given; the biological half-life of heparin, depending on the dosage, lies between 90 min and 5 h.

Low Molecular Weight Heparin (LMW Heparin)

Trade names or code numbers: Fragmin or Kabi 2165 (Kabi); heparin-NM-dihydergot (Sandoz); CY 216 (Choay; Midi-Labaz); PK 10169 (Pharmuka Laboratories).

Low molecular weight heparins (LMW heparin) are obtained through chromatographic procedures and also the chemical and enzymatic depolymerization of unfractionated heparin (UF heparin). The molecular weight range of the LMW heparins, 2,000–12,000 Daltons. The mean molecular weight of the various preparations lies between 3,500 and 8,000 Daltons, corresponding to about 11–27 saccharide units (molecular weight ca. 300 Daltons per unit of sugar). For the binding of heparin to antithrombin III, a penta-saccharide of a certain sequence is sufficient (N-acetyl-glucosamine-glucuronic acid —N-sulfate-3-O-sulfate-glucosamine— 2-O-sulfate-iduronic acid — N-sulfate-glucosamine-6-sulfate).

With the heparin-induced increase in the inhibition of Factor Xa (and Factor XIIa) through antithrombin III (AT III) it is probable that only a binding of heparin to AT III is necessary. For the inhibition of Factor IIa (and also IXa and XIa) however, a simultaneous binding of heparin both to antithrombin III and thrombin (IIa) seems to be

necessary. For this reason a chain length of 8 to 16 sugar units is sufficient for the AT III-mediated inhibition of Factor Xa through heparin – depending on the degree of sulfatization. A chain length of over 18 sugar units is a precondition for the effective inhibition of Factor IIa. This explains the anti Xa action of the LMW heparins, with only a slight influence on the activated partial thromboplastin time (aPTT) and thrombin time (TT), in contrast to the UF heparins, which besides their anti Xa activity also prolong the aPTT and TT through a simultaneous anti IIa action. LMW heparins do not influence thrombocyte function. It was hoped that with the LMW heparins greater antithrombotic protection would be achieved and at the same time less of an anticoagulatory and hemorrhage-promoting effect.

By definition the activity of 1 mg of the International Heparin Standard corresponds to 130 International Units (I.U. ≙ USP units) – regardless of the method of determination used. For the determination of the activity of heparins, inter alia the following in vitro methods are used, in relation to one of the international standards, and the results are expressed in international units in each case:

1. the influence on the clotting time of recalcified sheeps' plasma (USP units; original method)
2. the anti Xa action (chromogenic substrate; clotting methods of Yin and Wessler);
3. the anti aPTT activity and
4. the anti IIa activity (chromogenic substrate; thrombin time).

UF heparins have an activity of 130 to 170 I.U./mg. The activities for anti Xa and anti aPTT are the same, i.e. the ratio is 1:1. With LMW heparins the anti aPTT activity is about 4 times less than the anti Xa activity. The ratio of anti Xa to anti aPTT is 3:1 to 4:1 (e.g. Fragmin: 160 I.U. anti Xa/mg ≙ 40 I.U. anti aPTT/mg; CY 216: 200 I.U. anti Xa/mg ≙ 50 I.U. anti aPTT/mg). The anti Xa activities in relation to the weight unit lie in the same order of magnitude with UF and LMW heparins.

The ratios obtained in the in vitro determinations of activity do not correspond to those ex vivo. This applies both for the individual methods of determination and also for the comparison of UF with LMW heparin using the same kind of determination procedure. The bioavailability for LMW lies over 80%, for UF heparin at 15–20%.

The biological half-life (anti Xa action) after subcutaneous administration is 240 min for LMW heparin independent of the dose, and after intravenous administration it is 120 min; the figures for UF heparin are 120 min and 60 min respectively. With subcutaneous and intravenous administration of the same activities in I. U. anti Xa, higher activities are measured ex-vivo with LMW heparin compared with UF heparin in each case. Given the same dose the antithrombin III level shows a less marked fall under therapy with LMW heparin than under UF heparin.

No generally accepted dosage guidelines exist yet. For prophylaxis against thrombosis the dose lies at 1,500 to 1,850 I. U. anti aPTT and correspondingly at 5,000 to 7,500 I. U. anti Xa/day. A single daily administration seems to be adequate. For the treatment of thrombosis 10,000 to 20,000 I. U. anti Xa given subcutaneously or intravenously as a continuous infusion are recommended. The maximal heparin activities measured ex vivo lie roughly between 0.3 to 1.0 I. U. anti Xa 2 to 3 hours after administration, with subcutaneous administration they lie at 0 to 0.03 I. U. after 18 to 24 hours. Surveillance by means of the aPTT and the thrombin time is not possible. They are only slightly prolonged. For this reason a comparison of therapy with unfractionated heparins, where the anticoagulation is monitored by means of the aPTT or the thrombin time, is hardly possible.

For anticoagulation in hemodialysis and hemofiltration a bolus injection of 30 to 35 I. U. anti Xa/kg bodyweight followed by 10 to 15 I. U. anti Xa/kg and hour is recommended for patients with a low risk of hemorrhage; in patients at risk of hemorrhage the corresponding figures are 5 to 10 I. U. anti Xa/kg as a bolus and 4 to 5 I. U. anti Xa/kg and hour.

Protamine

Protamine is a basic protein. It combines with heparin and inactivates its anticoagulatory action. Protamine is available as protamine hydrochloride and protamine sulfate. 0.7–1.5 mg protamine inactivates 1 mg unfractionated (UF) heparin, that is, 130–170 I. U. heparin. Protamine hydrochloride is preferentially used. 1 ml protamine hydrochloride 1,000 or 5,000 (Roche) inactivates *in vitro* 1,000 I. U. or 5,000 I. U. UF heparin. By the heparin rebound effect one understands a

reappearance of the anticoagulatory heparin action *in vivo* after initial complete neutralization of the action by protamine. This is conditioned by the fact that the heparin-protamine complex is dissociated and protamine is eliminated more rapidly from the circulation than heparin. Moreover, protamine is an antithromboplastin and inhibits the reaction between thromboplastin, prothrombin and calcium. It therefore has an anticoagulatory action on sole administration or as an overdose. The additional protamine effects mentioned are to be considered in neutralization of heparin *in vivo*. With intravenous heparin therapy protamine hydrochloride is injected i.v. in an amount which corresponds to 50–75% of the last heparin dose given, or infused in the last 12 h. Further protamine injections may need to be given under control by thrombin time or partial thromboplastin time. This is especially true in the case of subcutaneous heparin administration, with the heparin from the depot and the vascular endothelium flowing back into the circulation over several hours. One unit of protamine chloride neutralizes about 1 I.U. anti-aPTT of low molecular weight (LMW)heparin. 40% to 50% of the anti Xa activity is still retained.

Coumarin Derivatives

The coumarin derivatives available in the FRG are monocoumarols (phenprocoumon= Marcumar; acenocoumarol = Sintrom; warfarin = Coumadin). The coumarin derivatives inhibit the vitamin K epoxyreductase (Fig. 3/I and 1/IV). Thereby the vitamin K dependent carboxylation in the gamma position of the glutamic acid of the protein of the prothrombin complex is inhibited. The calcium binding which is dependent on this and which is necessary for the function of the protein, becomes impossible. The functionally inactive precursors of the coagulation factors, which are described as PIVKA (PIVKA = *p*rotein *i*nduced by *v*itamin *a*bsence or *a*ntagonists) circulate in the plasma. Starting the treatment with phenprocoumon (Marcumar) in a decreasing dosage in the first 2–3 days 6–10 tablets are given in total, corresponding to 18–30 mg. After 4–5 days the therapeutic range of the prothrombin time is reached. The daily maintenance dose is ½–2 tablets, occasionally smaller or higher doses are necessary. With acenocoumarol (Sintrom) the total dose within the first 2–3 days lies between 6–12 tablets, corresponding to 24–48 mg. The maintenance

Table 1. Characteristics of some oral anticoagulants

Trade name	International designation	Content per tablet (mg)	Initial dose (tablets) 1st	2nd day	Maintenance dose (tablets/day)	Effect beginning (hours)	Normalization of prothrombin time after withdrawal (days)	Plasma half-life (hours)
Marcumar (Roche)	Phenprocoumon	3	4–6	2–4	½–2	48–72	7–14	160
Sintrom (Geigy)	Acecoumarol	4	5–7	2–4	½–3	36–48	3–8	8
Coumadin (Merrell)	Warfarin	5	5–8	3–5	1–3	36–48	4–6	45
Tromexan (Geigy)	Ethyl bis-coumacetate	300	4–6	2–3	½–3	18–30	3–5	2

dose from the 4th–6th day on lies between ½ and 3 tablets (Table 1). After withdrawal of the therapy the prothrombin time or Quick value normalizes itself with phenprocoumon (Marcumar) within 7–14 days, with acenocoumarin (Sintrom) after 3–8 days. However, the hemostasis normalizes earlier, with Quick values around 50% of the normal, so that an elevated bleeding tendency no longer exists. Guidelines for the preparation of patients for diagnostic and therapeutic interventions as well as for the interruption of an oral anticoagulant therapy in the case of bleeding are given in Table 2 and Table 3. The vitamin K_1 content of the food probably plays no role, or only a subordinate role in variations of the Quick values under oral anticoagulation, although cabbage and spinach contain relatively large amounts of vitamin K_1 (Table 4).

Table 2. Preparation of patients treated with indirect anticoagulants for diagnostic and therapeutic interventions

Intervention	Preparation	Quick value aimed at
Tooth extraction	2–3 days therapy pause	30%
Minor operation Arteriography	3–6 days therapy pause or 3–5 drops Konakion	> 40%
Major operations Translumbar aortography	5–10 drops Konakion perhaps PPSB	> 60%

30 drops = 1 ampoule Konakion = 10 mg vitamin K_1

Table 3. Guidelines for the treatment of patients under therapy with coumarin derivatives showing hemorrhages of different extent

Indication	Precautions	Beginning of effect
Slight bleeding	Cease anticoagulants	1 day–2 weeks
Moderate bleeding	3–10 mg Vit K_1 30 drops = 1 ampoule Konakion = 10 mg	after 6 h
Massive	3–10 Amp PPSB (500 IU) and 10 mg = 1 amp Vit. K_1	Immediate

Table 4. Vitamin K content of foods (Jaenicke 1982)

100.0 g contains	mg Vitamin K
Hen or goose egg	0.02
Cow's milk	0.002
Liver (Cod)	0.1
Liver (Cow, Sheep)	0.2
Liver (Pig)	0.4–0.8
Muscle	0.1–0.2
Peas	0.1–0.3
Strawberries	0.1
Potatoes	0.1
Chestnut leaves	6.0
Types of Cabbage (Savoy, Green Cabbage)	3.2
Stinging Nettle	1.6–3.2
Spinach	3.0–4.6
Green Tomatoes	0.8
Red Tomatoes	0.4

Vitamin K_1

Proprietary name: Konakion. Vitamin K_1, which is available from plant sources, is on the market as Konakion in 0.5 ml ampoules corresponding to 1 mg Konakion, and in 1 ml ampoules corresponding to 10 mg. It is dispersed in colloidal aqueous solution with the help of an emulsifier and contains 2.5 mg per ampoule phenol as a conserving agent. With mild hemorrhage as a consequence of treatment with coumarin derivatives and only moderate depression of the Quick value below the therapeutic range, the breaking off of therapy without or with oral administration of 1–5 mg Vitamin K is sufficient (Table 3). With threatening hemorrhage and larger overdose of coumarins the single i. v. dose of vitamin K_1 amounts to 10–20 mg. The daily dosage should not exceed 40 mg. The injection must be carried out slowly, because in rare cases circulatory reactions up to shock occur. An increase of coagulation-active factors of the prothrombin complex in the blood, measurable by a shortening of the thromboplastin time or an increase of the Quick value, is to be expected after 3–6 to 8 h. Too large amounts of Konakion should not be injected because a new adjustment of therapy with oral anticoagulants is made more difficult.

The immediate normalization of the coagulation is to be obtained by infusion of prothrombin complex preparations or fresh frozen plasma.

Streptokinase

Proprietary name: Streptase, Kabikinase. Streptokinase is a protein with a molecular weight of 47,000 Daltons. It is eliminated from the circulation with two clearance rates. The half life of the more rapid component amounts to 18 min, that of the slower to 83 min. Streptokinase binds to plasminogen in a molar proportion of 1 : 1 to form the so-called streptokinase-plasminogen activator complex. The plasminogen molecule associated with streptokinase undergoes a conformational change and displays an enzymatic activity corresponding to that of plasmin. The activator complex transforms further plasminogen molecules present in the circulation into plasmin, during which on the basis of *in vitro* investigations in a molar proportion of activator complex and free plasminogen of 1 : 10 the highest lytic potency is to be obtained.

At the beginning of the streptokinase treatment, the anti streptokinase must be neutralized; depending on past streptococcal infections or streptokinase treatment only a short time previously, it my show variably high titers. The amount of streptokinase which neutralizes the antistreptokinase titer is determined, either by means of the so-called "titratable initial dose", or on the other hand the initial streptokinase dose is chosen so, that the antistreptokinase is certainly neutralized. In recent years the mean population antistreptokinase titer has decreased, so that an initial dose of 250,000 I.U. streptokinase is sufficient in over 90% of cases. Also, with initial incomplete neutralization of the antistreptokinase a lysis defect is present, which presumably depends on the fact that streptokinase is in part bound to antistreptokinase and in part to plasminogen. During streptokinase therapy the antistreptokinase titer increases after 3–5 days, so that the therapy becomes ineffective. After successful treatment the titer has decreased after 3–6 months, so that a new streptokinase therapy is possible. In the early phase of streptokinase therapy there occurs a period of plasminemia in which the inhibitior potential of the plasma is overcome. Depending on the streptokinase dosage the plasminemia can last several hours, only to fade away in the further course, with

decrease of the circulating plasminogen. In the initial phase a hypercoagulability can be observed, It is produced through a specific plasmin-induced activation of coagulation factors V and VIII. By coagulation analysis a transitory shortening of the recalcification time and the partial thromboplastin time, an increased activity of Factor V and VIII and under some circumstances a positive ethanol test are detectable.
The fibrino(geno)lytic effect measurable in the plasma in the further course of a streptokinase therapy, is identified by the prolongation of the thrombin and reptilase times, the decrease of fibrinogen, Factor V and VIII and the increase of fibrin/fibrinogen cleavage products, and is dependent on the actual relationship of activator complex to free plasminogen which is available for plasmin formation. With lower streptokinase doses under 50,000 I.U./h the plasminogen in the plasma is moderately reduced. The content of activator complex is small, the plasmin formed is moderately high, and the measurable lytic effect depending on the available antiplasmin activity is small to medium grade. With medium dosage around 100,000 I.U./h the plasminogen content of the plasma is clearly lowered, the activator concentration is high, the plasmin content high, the fibrino(geno)lytic effect clear. With higher doses of 150,000 I.U./h and above the plasminogen content in the course of therapy is mainly under 5% of the norm, the activator content is very high, free plasmin minimal to not present, and the demonstrable coagulation disorder in the systemic blood small. After interruption of the streptokinase administration after about 1–2 h no further plasmin activity is detectable. The changed coagulation analytical parameters normalize themselves within 24 h.
Therapeutic proposals of high streptokinase doses in a short time anticipate an effect either through the transitory plasminemia or by utilizing as much of the plasminogen as possible in, primarily, an endolysis of the activator complex, while largely avoiding the systemic lysis effect of plasma. A possible danger in fibrinolysis with high streptokinase doses is seen in the fact that fresh thrombi, which may possibly form again at the end of fibrinolysis treatment may be poor in plasminogen and therefore lysable with difficulty.
The standard dose is 250,000 I.U. streptokinase initially within 20 min, with subsequent infusion of 100,000 I.U/h. In the so-called adjusted lysis ⅔ of so-called "titratable thrombolysis initial dose" (TID) given initially is infused hourly. With lung embolism 500,000

I. U. initially is recommended (Table 6). With acute myocardial infarction besides streptokinase treatment extending over 1–2 days with standard dosage, activator lysis with 1.2–1.5 million I. U. streptokinase lasting over 90 min is set up, which has as its objective a thrombolysis in the occluded coronary vessels. In intracoronary thrombolysis after acute myocardial infarction 120,000–2500,000 I. U. are locally injected over 60–90 min at the angiographically identified occlusion in the vessel.
If the lysis effect measured in the systemic blood is very pronounced and if there exists a danger of hemorrhage increased activator complex may be induced through increase of the streptokinase dose, whereby a lowered supply of plasminogen is available for conversion into plasmin. By elevation of the streptokinase dose the systemic lysis effect may thus be reduced. Conversely, in suitable cases, the systemic lysis may be increased by lowering of the streptokinase dose.

Urokinase

Proprietary names: Actosolv, Rheothromb, Ukidan, Abbokinase or Urokinase with attached name of firm.
Urokinase is a serine protease which is obtained either from human urine or from tissue culture of embryonic human kidneys. It exists in a high molecular form (molecular weight 54,000 Daltons; HMW UK) and a lower molecular weight form (molecular weight 33,000 Daltons, LMW UK).
The higher molecular weight form has a higher potency to transform plasminogen into plasmin, where this effect is clearer in native plasminogen (Glutamine-plasminogen) than in partially degraded lysine-plasminogen, which lacks the N-terminal section of native plasminogen.
With a test system in which the time required for the dissolution of a standardized clot is taken as a basis, the lytic effect is approximately the same. With the commercially available urokinase preparations, both forms are present in each case in different mixture proportions depending on the method of preparation. Here also the differing fibrinolytic potencies of the preparations from different suppliers is to be seen as compared with streptokinase. The half-life of urokinase amounts to about 14 min. *In vivo* infused HMW urokinase is rapidly

Table 5. Standard doses and supervision of fibrinolysis with streptokinase or urokinase

	Streptokinase	Urokinase
Initial dose I.U.	100,000–250,000 –500,000	250,000–600,000
Maintenance dose I.U.	100,000–150,000	80,000–150,000 –250,000
Heparin I.U./24 hr	10,000–25,000 in addition if thrombin time < 40 sec.	
Supervision	Thrombin time Reptilase time Fibrinogen (Partial thromboplastin time, Quick)	

transformed by proteinases of the plasma into LMW urokinase, so that only this becomes therapeutically active. Urokinase is not antigenic. The kinase inhibitors present in plasma must be overcome by the initial dosage. The substance can be administered over long periods of time. A streptokinase treatment which is no longer possible can be continued with urokinase.

The dosage details for the individual indications vary considerably. They lie between 100,000–600,000 I.U. initially within 10–20 min, and 40,000–300,000 I.U./h corresponding to 1 million I.U. to 7.5 million I.U./day. On account of the usually small fibrino(geno)lytic effects in the systemic blood under the usual dose regime of 40,000–150,000 I.U./h in the less acute thrombotic events the simultaneous administration of 500–1,000 I.U. heparin/h is recommended. In pulmonary embolism the therapeutic recommendations are 300,000–600,000 I.U. initially and 300,000 I.U./hour over 12–24 h. In myocardial infarction 300,000–600,000 I.U. is given initially and 200,000–250,000 I.U./h over 10–12 h is infused (Table 5).

Prourokinase

Prourokinase is formed in the cells of numerous tissues, including in particular the kidneys. It is a single chain molecule (single

chain urokinase plasminogen activator ≙ sc-uPa). It consists of 411 amino acids and has a molecular weight of 54,000–55,000 Daltons. The plasma concentration amounts to 5–10 µg/l, the biological half-life to about 9 min. It is relatively stable in the plasma and is not bound by inhibitors (in contrast to urokinase, which is inhibited through antithrombin III, $alpha_1$-antitrypsin, and $alpha_2$-macroglobulin). No proteolytic activity of sc-uPA can be demonstrated in the plasma. sc-uPA exhibits a so-called kringle structure with an affinity to fibrin (Fig. 1).

Through limited plasmin-induced splitting of a peptide bond (Lys_{158}-Ile_{159}) the two-chain molecule linked by a disulfide bridge, HMW-urokinase develops (two chain-uPA = tc-uPA). The molecular weight remains the same. The light chain (20,000 Daltons) of tc-uPA carries the fibrin affinity, the heavy chain (34,000 Daltons) the active site. Through the proteolytic splitting of sc-uPA with the formation of tc-uPA, the fibrin affinity decreases. The fibrin-specific proteolytic activity remains the same.

The absence of proteolytic activity with prourokinase (sc-uPA) in the plasma and the affinity to fibrin, make prourokinase of interest as a thrombolytic substance. The clinical trial is still in its initial stage.

Tissue Plasminogen Activator

*T*issue-type *p*lasminogen *a*ctivator (tPA) is contained in the cells of numerous organs, in particular also in the vessel wall. It is released from the vessel wall by various stimuli (incl. thrombin, venous occlusion, DDAVP infusion). tPA is a serine protease, consists of 527 amino acids with 15 disulfide bridges, has a carbohydrate content of 9.5% and a molecular weight of 70,000 Daltons. tPA molecules with a somewhat lower molecular weight occur during the isolation process through proteolytic degradation in the absence of aprotinin.

The plasma concentration amounts to 6 to 7 (up to 10) µg/l and increases, e.g. after venous occlusion, to about 20 to 80 µg/l. The biological half-life is 3 to 5 minutes. Only a slight proportion of the tPA circulates in the plasma in free from; it is mostly bound to the inhibitors $alpha_2$-antiplasmin, $alpha_1$-antitrypsin and to a special, rapidly reacting tPA inhibitor. tPA occurs in the plasma as a single chain molecule (single chain tPA ≙ sctPA) which, in contrast to other serine proteases

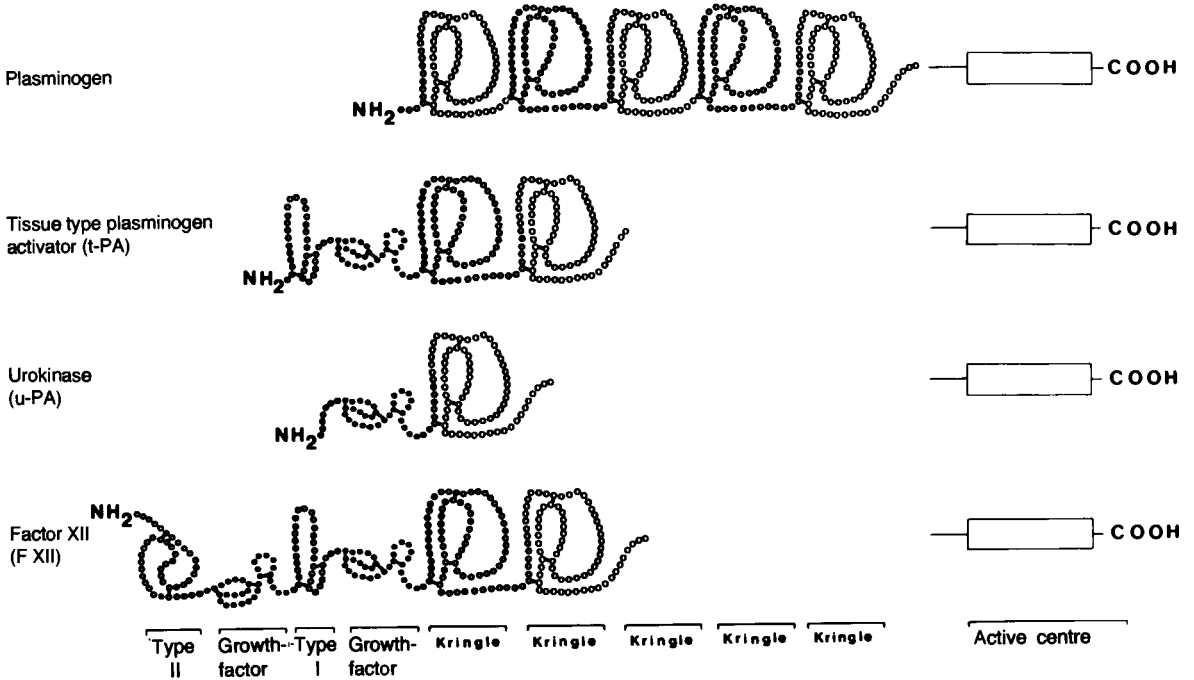

Fig. 1. Structure of plasminogen, tPA, urokinase and Factor XII

already has proteolytic activity. Through limited plasmin-catalyzed splitting (Arg_{275}-Ile_{276}) tPA is converted into a two chain molecule linked by disulfide bridges (two chain tPA ≙ tc-tPA). The heavy (A) chain consists of 275 amino acids (molecular weight 40,000 Daltons), the light (B) chain of 252 amino acids (molecular weight 30,000 Daltons). The heavy chain contains two so-called kringle structures, such as other serine proteases also display (e. g. plasminogen with 5 kringle structures) and a so-called finger structure such as occurs with fibronectin (Fig. 1). These structures mediate the affinity to fibrin. The light chain contains the active site of the enzyme. tPA converts plasminogen into plasmin through the splitting of a peptide bond (Arg_{560}-Val_{561}). With the concentration of tPA present in the plasma plasmin formation and fibrinogenolysis do not take place in the aqueous phase. tPA – like plasminogens have a high affinity to fibrin via their lysine binding sites (kringle structures). If a thrombus develops, a trimolar complex forms in that tPA converts plasminogen to plasmin, the proteases are largely withdrawn from their inhibitors and plasmin specifically degrades fibrin. It is upon this phenomenon that the selective lysis of fibrin clots and thrombi with no or only slight systemic fibrinogenolysis, used therapeutically, is based.
The studies carried out to date on thrombolysis after acute cardiac infarction made use of an infusion of tPA in a dose of 0.75 mg/kg bodyweight given over 90 min and 80 mg given over 3 hours.

Acyl Enzymes

With the aim of increasing the thrombolytic action of fibrinolytic agents whilst at the same time reducing the systemic fibrinogenolysis, the active center of fibrino(geno)lysis-specific enzymes and their activators was reversibly blocked by esterification with acylating substances. To date the most detailed investigations have been carried out on the acylated activator complexes p-anisoyl-streptokinase-lys-plasminogen (BRL 26921) and 4-aminobenzoyl-streptokinase-lys-plasminogen (BRL 33575). After intravenous injection the complexes are initially inactive. The fibrin affinity of the plasminogen (kringle structures) remains uninfluenced in the complexes. Because of the fibrin affinity of the plasminogen kringle structures, the complex settles down on the thrombus. During the slow deacylation the complex can

convert fibrin-bound plasminogen to plasmin, which, protected from inhibitors, lyses the thrombus.
BRL 26921 deacylates with a half-life of ca. 40 minutes, BRL 33575 with a half-life of ca. 17 hours. As a measure for the clearance of the complex from the circulation in man the functional half-life for BRL 26921 is ca. 60 min (18 to 70 min) and for BRL 33575 ca. 7 hours.
The expectations placed in these substances have not been completely fulfilled. After the injection of 5 to 10 mg BRL 26921 there is a progressive reduction in fibrinogen, plasminogen and alpha$_2$-antiplasmin in the plasma. Bleeding, mostly from puncture sites, was observed in up to 40% of those treated.
Some clinical trials with BRL 26921 (sometimes also with BRL 33575) with positive results are available. In cases of pulmonary embolism 3×5 or 10 mg was given at 8-hour intervals for 24 hours. In deep vein thromboses 5 or 10 mg were successfully used as a bolus or short-term infusion at 8 to 12-hour intervals over 2 to 10 days. In myocardial infarction 5 to max. 30 mg were given as a bolus by both intracoronary and systemic administration. It was reported that 60 to 70% of the occluded coronary vessels were recanalized in the course of the first hour after the start of therapy.

Aprotinin

Proprietary name: Trasylol, Antagosan. Aprotinin is a polyvalent protease inhibitor with a molecular weight of 6,500 Daltons. Aprotinin binds itself with the enzyme in a reversible 1:1 complex. It inhibits fibrinolysis by inactivation of plasmin, the kallikrein-kinin system as well as the coagulation system by the inhibition of Factor XII$_a$ and further serine proteases. However, the latter action is weak. With spontaneous hyperfibrinolysis and fibrinolytic conditions as a consequence of streptokinase or urokinase therapy, the usual dosage for inhibition of the lysis effect is 500,000 KIU initially, injected over several minutes, with a subsequent long term infusion of 50,000 KIU to 100,000 or 200,000 KIU/h maximal over several hours. Alternatively a dose of 300,000 KIU can be injected every 2–4 hours.

Table 6. Dosage guidelines for antifibrinolytics (Abbreviations see text)

Preparation	Dosage	
	Initial	Maintenance
EACA	4–6 g	12 g–24 g/24 hour
AMCHA	0.5 g	1.5 g–4.5 g/24 hour
PAMBA	0.1–0.3 g	0.2 g–0.6 g/24 hour
Aprotinin	500,000 KIU	50–100,000 KIU/24 hour

Synthetic Antifibrinolytics

Available are epsilonaminocaproic acid, 4-aminomethyl-cyclohexane carboxylic acid (AMCHA, Tranexamic acid; Anvitoff, Zyclocapron, Ugurol) and paraaminomethylbenzoic acid (PAMBA: Gumbix) These substances inhibit the transformation of plasminogen to plasmin, and to a smaller extent the action of plasmin. With hyperfibrinolysis the initial dose of epsilon-aminocaproic acid is 4–6 g with subsequent administration of 2 g every 2–6 h, according to the effect. The maximal daily dose is 12–24 g. The initial dose of AMCHA is 0.5 g, with PAMBA between 0.1–0.3 g, with subsequent administration of 1.5–4.5 g or 0.2–0.6 g/day in divided doses. Intravenous injection and oral administration in tablet forms are possible, in which the total intravenous dose is somewhat lower than the oral dose (Table 6).

Blood Components (Table 7)

Fresh Plasma

Fresh plasma and fresh frozen plasma contain the coagulation factors and their inhibitors in unactivated forms and in physiological concentrations. A unit of a coagulation factor is defined as that amount which is present in 1 milliliter of plasma from a donor pool of at least 10 healthy persons. It corresponds to an activity of 100%. Because the plasmas are obtained from individual donors, the risk of hepatitis is rather small. Because no concentration of the factors takes place, a relatively high transfusion volume is necessary for the achievment of a

Table 7. Characteristics of transfused coagulation factors and their least hemostatic concentrations (Cash 1982)

Factor	Synonym	Minimal hemostatic concentration (% of norm)	Half-life of transfused factors (Optimal conditions)	Recovery in blood in % transfused (Optimal conditions)	Stability in whole blood 4 °C
I	Fibrinogen	10–25	4 days	50	Stable
II	Prothrombin	40	3 days	40–80	Stable
V	Proaccelerin	10–15	12–15 h	?80	Unstable
VII	Proconvertin	5–10	4–6 h	70–80	Stable
VIII	Antihemophilic Factor (AHF)	10–40	12–15 h	50–80	Unstable
IX	Christmas Factor	10–40	20 h	25–50	Stable
X	Stuart Power Factor	10–15	2 days	50	Stable
XI	Plasma thrombo-plastin antecedent (PTA)	30 ?	3 days	90–100	Stable
XII	Hageman Factor	?	?	?	Stable
XIII	Fibrin stabilising	1–5	6 days	?5–100	Stable
Platelets	Factor	5–10	4 days	29–45	Unstable

hemostatic concentration. Concerning fresh blood, fresh frozen plasma, and platelet concentrate, the corresponding chapter should be referred to.

Cohn Fraction I

The Fraction I according to Cohn's classification contains, depending on the supplier, 400–1000 mg fibrinogen and 100–300 U Factor VIII in 100 ml. Von Willebrand Factor and Factor XIII are also contained in the preparation.

Factor VIII Preparations

In cryoprecipitates the coagulation Factor VIII is enriched 2–5–10 times the normal. The transfusion volumes are correspondingly smaller. Cryoprecipitates also contain fibrinogen and Factor XIII and can be used for the substitution therapy of deficiencies of these factors. On account of their high content of von Willebrand factor activity, in addition to their value in substituting Factor VIII, they are especially useful for the correction of the platelet defect and prolonged bleeding time in the von Willebrand-Jürgens syndrome. Purified Factor VIII preparations are only of limited value. Because the cryoprecipitates are obtained from a small donor pool, the danger of hepatitis is only moderately high.
Factor VIII concentrates are prepared in medium and high grades of purity. The Factor VIII concentration amounts to 25–50 times the normal. The injection volumes lie between 10–30 ml for 250–1,000 U. Because these concentrates are obtained from a donor pool of 1,000 and more persons, the danger of hepatitis, despite transaminase determination and radioimmunological exclusion of a hepatitis-B infection of the individual donors, before fractionation and in the end product is very great. By special heat processing it has become possible to prepare concentrate preparations in which, whilst the Factor VIII activity is retained, the hepatitis infection is excluded, or the danger of an infection is small (Factor VIII–HS, Behringwerke; Factor VIII – HT, Hyland). The concentrate corrects the Factor VIII deficiency in von Willebrand-Jürgens syndrome, however it removes only to a

limited extent the platelet defect and therewith the prolonged bleeding time.
For the treatment of hemophilia A with the presence of an inhibitor several preparations are available. Factor VIII of the pig (Speywood) acts as an animal protein antigen and can be decreasingly active after about 8–10 days.

The hemostasis defect due to Factor VIII inhibitor can be corrected by the use of prothrombin complex preparations in which a partial activation of the factors has taken place during preparation (Konyne, Medac). With the preparation FEIBA (Immuno) and Autoplex (Hyland, Travenol) two special limited activated prothrombin complex preparations are available, which can be successfully used with inhibitors. A FEIBA (*f*actor *e*ight *i*nhibiting *b*ypass *a*ctivity) Unit is defined as activity which shortens the activated partial thromboplastin time of a Factor VIII-inhibitor plasma (Immuno) to half the initial value. The so-called "Factor VIII Correctional Unit" of Autoplex is defined as that activity of the preparation which shortens the partial thromboplastin time activated by ellagic acid to 35 s, by addition to a similar volume of Factor VIII – deficient plasma or Factor VIII – inhibitor plasma using Dade reagents. An Autoplex unit corresponds *in vitro* to about 1.5–2.0 FEIBA U. *In vivo* this difference possibly does not reach significance.

Factor IX Preparations

For the treatment of hemophilia B and of deficiency conditions of factors II, VII and X prothrombin complex preparations are available. The enrichment of the factors amount to 20–25 times the norm. Due to differences in preparation procedures the preparations do not contain all the factors in the same activity. They are especially poor in Factor VII. The activity data then relate to Factor IX. A specific partial prothrombin complex (Immuno) contains exclusively the Factors II, IX, and X. The newer products are said to no longer contain partially activated coagulation factors. Nevertheless, as a rule heparin and/or antithrombin III are added to them to avoid activation of coagulation. Moreover pure Factor IX preparations are available. These are enriched to 50–100 times the norm. By treatment with beta-prop-

ionolactane and UV radiation (cold sterilization) or heat treatment preparations are available, which are said to be safe from hepatitis).

Dosage Guidelines

(See also Chapter IV, Hemophilia A and Hemophilia B)

Factor VIII Preparations

The level of the necessary plasma concentration as well as the duration of substitution therapy in hemophilia A is dependent on the severity and extent of the injury or operation. The recovery after administration of Factor VIII, measured 15 min after injection, is between 50–80%. The half-life proceeds in 2 phases. The first phase lasts about 6 h; in it the distribution of Factor VIII into extravascular space is assumed. The subsequent slow phase amounts to 12–13 h. A unit of Factor VIII/kg body weight leads to an increase of factor VIII activity in the plasma of 1–2%. The initial dose is calculated from the desired increase in factor multiplied by the body weight in kg. Substitution is continued towards the end of the half-life period after about 8 h, with ½–¾ of the initial dose. With planned operations it is recommended to give the first injection several hours before the beginning of the operation. With extensive operations or injuries the turnover of Factor VIII is increased, so that the maintenance dose under some circumstances must be repeated after 2–6 h. With the von Willebrand-Jürgens Syndrome the Factor VIII activity increases further and remains for a longer time at a higher level than the amount infused and the half-life would lead one to expect. With long-term treatment a mean of 30–45 U/kg and week are necessary, which is administered in 2–3 divided doses. The total annual consumption of Factor VIII per patient is according to the severity of the hemophilia A and form of substitution between 50,000 and 200,000 U. The coagulation analytical control is carried out by means of Factor VIII determination and the partial thromboplastin time.
With inhibitor hemophilia the therapy depends on whether it is a case of so-called "low responder" or "high responder" (Table 5/IV). In the first case the inhibitor titer is from under 5 to a maximum of 10

Bethesda units, and increases under therapy to no higher than 10 Bethesda units. These cases, besides therapy with activated prothrombin complex, can alternatively be treated with high dose Factor VIII.

With the "high responders" with an inhibitor titer of over 10 Bethesda units and an anamnestically known increase under Factor VIII therapy of several hundred Bethesda units, prothrombin complex preparations are indicated. Depending on the extent of the hemorrhage, 50 U–100 U/kg body weight of FEIBA and Autoplex are initially given. The repeated injections depend on the clinical result and are necessary every 6–8 to 12 h. Alternatively Konyne can be given. The Factor VIII bypass activity seems to be dependent on a sufficient number of platelets in the blood, through which the necessary complementing procoagulatory activities are available. Below a platelet count of 100,000/mm^3 the clinical effect of the activated prothrombin complex decreases. The control of therapy is carried out using the decrease of full blood coagulation time, the shortening of the r-time in the TEG, and to a certain extent by the activated partial thromboplastin time. The Factor VIII level does not increase according to expectations. The coagulation-analytical findings and the clinical results do not correlate, which has to be taken into consideration controlling the treatment.

Factor IX and Prothrombin Complex Preparations

The principle of treatment corresponds to that of hemophilia A. The recovery of Factor IX amounts 15 min after injection to only 20–50%. The half-life time is initially about 4.5 h and in the second phase 18–38 h. On the basis of the low recovery one must expect after injection of 1 unit Factor IX per kg body weight a maximal activity increase in the plasma of 1%. Repeated injections are necessary every 12–24 h in ½ to ¾ the initial dose. With extensive hemorrhage or operations the subsequent injections must follow in a short interval. The coagulation-analytical control takes place by means of the activated partial thromboplastin time and the Factor IX determination. With the long-term treatment 9 U to 18 U/kg body weight 1–2 × per week are injected and in individual cases sometimes only once every 2 weeks. With Factor VII deficiency the short half-life of 4–6 h is to be taken

into account, and the fact that some prothrombin complex preparations contain Factor VII in small quantities.
With extensive hemorrhage the half-life can be shortened to 30 min. Higher blood levels of Factor VII than 20–30% are usually not necessary. The recovery is high. A unit of Factor VII/kg body weight elevates the activity in the plasma by about 2% or the Quick value about 1%. In the equally rare Factor II and Factor X deficiencies repeated injections usually are only necessary once a day, due to the long half-lives.

Side Effects

In rare cases pyrogenic and allergic reactions occur. The transfer of hepatitis B or non-A, non-B hepatitis is very high in preparations obtained from large donor pools. Non-A, non-B hepatitis predominates. In the course of therapy however 60–90% of the patients are also HBs-antibody positive. After the first injections the hepatitis frequency amounts to 25%. Occasionally in blood groups A and B hemolytic anemias occur as a consequence of a contamination of the preparations with isoagglutinins. Isoagglutinin-poor concentrates are available. Inhibitors occur in hemophilia A in 5–20%. They occur especially in children with severe hemophilia and high substitution requirements, mainly during the first 100 transfusions. 30% of cases are "low responders". With hemophilia B the frequency of an inhibitor is about 1% of the patients. Under therapy with prothrombin complex preparations isolated venous thromboses, lung embolisms, thrombocytopenia and consumption reactions have been observed. The addition of heparin, and in individual preparations also of antithrombin III should avoid a coagulation activation.

DDAVP

Desmopressin (DDAVP = 1-desamino-8-D-arginine vasopressin) is a vasopressin analogue (Minirin). It liberates Factor VIII activity, Factor VIII antigen and von Willebrand Factor from the endothelium. It can be used in mild and moderate hemophilia A and von Willebrand-Jürgens syndrome. The Factor VIII activity increases to 2–3 times the

initial value. After some days there occurs an increasing loss of activity. DDAVP can therefore only be used in smaller wounds and operations with danger of hemorrhage of short duration, or it serves for the initial sparing of Factor VIII preparations in long-term substitution therapy. Because fibrinolytic activity is also liberated by DDAVP, the combination with an antifibrinolytic agent is to be recommended. DDAVP is initially infused at 0.4 μg/kg body weight within 20 min. The infusions are repeated every 12–24 hours.

Factor XIII (Fibrin Stabilizing Factor)

Proprietary name: Fibrogammin. The Factor XIII consists of 4 subunits (2a units and 2b units), with a molecular weight of 75,000–80,000 Daltons per subunit. The entire molecule has a molecular weight of 320,000 Daltons. Only the a subunits are enzymatically active and contained in the commercial preparation. The biological half-life amounts to 4.5 days. In congenital Factor XIII deficiency substitution therapy with 500–1,000 U at intervals of about 4 weeks is necessary. In hemorrhages which are due to Factor XIII deficiency, the administration of 2,500 U initially, with subsequent daily administration of 1,000–1,500 U until the cessation of bleeding is recommended.

Antithrombin III

Antithrombin III is a glycoprotein with 425 amino acid and 4 carbohydrate residues. The molecular weight was determined as 56–58,000 Daltons. The plasma concentration lies between 10–20 mg/100 ml. It binds in a 1:1 complex with the coagulation system serine proteases IIa and Xa as well as XIIa, XIa, IXa and VIIa. The reaction is strongly accelerated by heparin. As mentioned above, 1 μg antithrombin III inhibits 32 U Factor Xa, and correspondingly the activation of 1,600 U Factor IIa (thrombin) is inhibited. A unit of antithrombin III concentrate/kg body weight elevates the activity in the plasma by about 1% of the norm. The biological half-life amounts to about 2.5 days. In consumption coagulopathy it can be reduced to a few hours. The antithrombin III activity in the organism should be more than 80%.

For thrombosis prophylaxis about 1,000–2,000 U per day are required. The therapeutic dose for thrombosis, consumption coagulopathy and antithrombin III deficiency is initially 1,000–2,000 U, and a daily substitution therapy of 2,000–4,000 U, divided into several individual doses of 500 U. The heparin dose to be administered simultaneously is adjusted according to the thrombin time. With increased turnover controls of the antithrombin III-level are usually necessary.

Plasma Expanders

Dextran 60 and Dextran 40

Proprietary names: Macrodex 6%; Rheomacrodex 10%. In the studies of thrombosis prophylaxis dextran 60 has predominantly been used. Dextran 40 must have a similar action. The molecular weight varies around the values of 60,000 or 40,000 Daltons. Dextran is broken down by dextranases in the body and about ⅔ is excreted through the kidneys. The half-life in the plasma lies between 6 and 8 h in the case of dextran 60, and for dextran 40 at about 3 h. The antithrombotic action is due to a so-called "coating" i.e. the mantling of the platelets with consecutive impairment of platelet functions, to a dextran-conditioned decrease of Factor VIII, as well as to the easier lysability of thrombi which develop in spite of dextran administration. Anaphylactic reactions occur in 0.008% of patients. They can be inhibited by previous injection of the hapten dextran 1000 (Promit). In the preoperative thrombosis prophylaxis 1000 ml dextran is administered during the operation, starting at the beginning of the anesthesia. A further 500 ml are given 4–6 h after the operation or on the following day, with an infusion time of about 4 h. A third infusion of 1,000 ml follows on the first or second postoperative day.

Hydroxyethyl Starch

Proprietary names: HAES-Steril, 6%; HAES-Steril 10%; Plasmasteril, Expafusin. Hydroxyethyl starch has been introduced for thrombosis prophylaxis. It is available as 6 and 10% solutions. Hydroxyethyl starch has an average molecular weight of 200,000 Daltons. (HAES-

Steril, 6%; HAES-Steril, 10%) and has a plasma half-life of 3–4 h. Hydroxyethyl starch with a mean molecular weight of 450,000 Daltons (Plasmasteril) has a half-life of about 6 h. It is broken down in the organism by amylase, and excreted predominantly by the kidney. Anaphylactoid reactions occur in 0.006%. The amounts for perioperative infusion in thrombosis prophylaxis correspond to those for dextran. Hydroxyethyl starch with a mean molecular weight of 40,000 Daltons (Expafusin) has not so far been used systematically in thrombosis prophylaxis.

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